NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

Contents:

Premeeting briefing

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

This premeeting briefing presents:

- 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.

COMMON ABBREVIATIONS (shaded rows contain comparator technologies)	
BOC	boceprevir
BSC	best supportive care
CC	compensated cirrhosis
CHC	chronic hepatitis C
D	dasabuvir
DAA	direct acting antivirals
DCC	decompensated cirrhosis
DCV	daclatasvir
GT	genotype
ICER	incremental cost-effectiveness ratio
LDV	ledipasvir
NC	no cirrhosis
OPR	ombitasvir/paritaprevir/ritonavir
PR	peginterferon and ribavirin
QALY	quality-adjusted life year
R	ribavirin
SMV	simeprevir
SOF	sofosbuvir
SVR	sustained viral response
TE	treatment-experienced
TN	treatment naïve
TVR	telaprevir
VEL	velpatasvir

Key issues (1)

Are the following comparators relevant for this appraisal?

- Boceprevir and telaprevir – both were excluded from the company analyses
- Peginterferon alpha plus ribavirin (PR) – its use in practice is diminishing for certain genotypes
- Daclatsavir+PR and simeprevir+PR in GT4 patients – both were excluded from the company base case and ERG unable to perform analyses including these regimens

Where applied, does the committee accept the use of similar modelling assumptions as for previous CHC appraisals?

- Combining mild and moderate disease into 1 health state (consistent with TA330 & TA363)
- Use of SVR rates from individual trials (not NMA)
- Utilities:
  - Health state utility values derived from Wright et al., 2006
  - SVR-related utility increment from Vera-Llonch et al. 2013 (consistent with TA330 & TA363)
    - Other appraisals used 0.05 from Wright et al. 2006 or trial data
  - Use of treatment-specific utility increments (consistent with TA330 & TA363); removing them has little impact on results
- HIV co-infection treated the same as mono-infection, therefore no separate subgroup analysis
- Not including re-infection and transmission in base case

Key issues (2)

What are the committee's views on other modelling assumptions (differences from other appraisals):

- Applying a utility increment for patients with DCC who achieved a SVR
- Faster progression of liver fibrosis in GT3 (genotype-specific TP from NC to CC health states)
  - is Kanwal et al. generalisable to the UK?
- Other assumptions about treatment-independent transition probabilities:
  - all transition probabilities except GT3 NC to CC health states independent of genotype
  - probability of death from the DCC health states with and without SVR inconsistent with previous appraisals.
  - probability of hepatocellular carcinoma compensated/decompensated cirrhosis from Cardoso et al. (0.0631); in previous appraisals the committee concluded this TP is between 0.014 (Fattovich et al.) and 0.0631 (Cardoso et al.)
- Including LDV/SOF+R as a comparator for treating DCC (LDV/SOF has an MA for DCC but is not recommended by NICE for DCC, or in combination with ribavirin)

What are the committee's views on the appropriateness of the ERG's analyses?

- Combining GT1a and 1b
- Presenting pairwise comparisons instead of a fully incremental analyses
- New base case: correcting transition probabilities, reinfection probability of 2.4%, no utility increment for SVR from DCC

Hepatitis C

- Blood borne (people who inject drugs major source ≈90%)
- 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 (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 peginterferon plus ribavirin regimens
  - In recent times, direct-acting antivirals (DAAs) with better efficacy and improved safety profile are being used

DETAILS OF THE TECHNIOLOGY	
Technology	Sofosbuvir-velpatasvir (Epclusa)
Marketing authorisation	Treatment of chronic hepatitis C virus (HCV) infection in adults • Any genotype (GT1–6) • Patients without cirrhosis, those with compensated cirrhosis and those with decompensated cirrhosis • People with HCV/HIV co-infection and recurrent HCV after liver transplant are eligible ○ No data for SOF/VEL after liver transplant
Mechanism of action	SOF: inhibits HCV non-structural protein 5B (NS5B) ribonucleic acid (RNA)-dependent RNA polymerase; VEL: inhibits HCV non-structural protein 5A (NS5A) protein
Administration	Oral, once daily for 12 weeks SOF/VEL is given in combination with ribavirin for people with decompensated cirrhosis. Adding ribavirin may be considered for people with genotype 3 with compensated cirrhosis *(the company submission did not present results for this combination for GT3).*
Acquisition cost	SOF/VEL 28 tablets: • List price: £12,993.33 • Commercial price discount: [redacted](commercial-in-confidence) Ribavirin 56 tablets: £246.65
Cost of a course of treatment	SOF/VEL 12 weeks: • Anticipated list price: £38,980 (list) • Commercial price discount: [redacted](commercial-in-confidence) SOF/VEL+RBV 12 weeks: • Anticipated list price: £40,089.93 (list) • Commercial price discount: [redacted](commercial-in-confidence)

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
GT2	P ± R	All	75, 106 & 200
	SOF + R	NC TN[c]; NC TE; CC TN[c]; CC TE	330
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
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
GT5/6	P ± R	All	75, 106 & 200
	SOF + PR	CC TN; CC TE	330
[a] If certain clinical criteria are met; [b] Only for significant fibrosis; [c] Only if IFN-ineligible/intolerant			
Treatment durations vary by genotype and subgroup (see marketing authorisations)			

COMPANY'S DECISION PROBLEM & DEVIATIONS FROM FINAL SCOPE			
	Final scope issued by NICE	**Company submission**	**Rationale for deviations**
Pop.	People with chronic hepatitis C: • who have not had treatment for chronic hepatitis C (treatment-naive) • who have had treatment for chronic hepatitis C (treatment-experienced)		
Int.	Sofosbuvir-velpatasvir		
Com.	• BSC (GT1-6) • BOC + PR (GT1 only) • DCV + PR (GT4; specific people) • DCV + SOF ± R (GT1 & 3 & 4; specific people) • LDV/SOF (GT1 & 4; specific people) • OPR ± D ± R (GT1 & 4) • PR (GT1-6) • SMV + PR (GT1 & 4) • SOF + R ± P (GT1-6; specific people) • TVR + PR (GT1 only)	As per scope, with exceptions: • BOC and TVR not included; extrapolated findings for SMV+PR • Some comparators included only in scenarios (eg DCV+PR and SMV+PR) • LDV/SOF a comparator for decompensated cirrhosis (has marketing authorisation in DCC but not recommended NICE) • Best supportive care = no treatment	BOC and TVR no longer representative of current clinical practice following approval of the newer DAA technologies DCV+PR and SMV+PR are not relevant to clinical practice for GT4 patients
Out.	• sustained virological response • resistance to treatment • mortality • adverse effects of treatment • health-related quality of life	Resistance not modelled	Resistance does not impact costs or QALYs

Company submission focussed on GT3 (unmet need)

Clinical effectiveness evidence

company submission chapter 4

Clinical evidence for SOF/VEL (1): 3 phase III randomised controlled trials

Trial	Int.	Comp.	Population	Sites	Design
ASTRAL-1	SOF/VEL 12 weeks	Placebo 12 weeks	• GT 1,2,4,5,6 • TN & TE • NC & CC	81 sites in USA, Canada, Europe (incl. 11 UK sites, n=104) and Hong Kong	Double blind 5:1 randomisation except GT5 (n=35, SOF/VEL only)
ASTRAL-2	SOF/VEL 12 weeks	SOF + R 12 weeks	• GT2 • TN and TE • NC & CC	51 sites in USA	Open label 1:1 randomisation
ASTRAL-3	SOF/VEL 12 weeks	SOF + R 12 weeks	• GT3 • TN and TE • NC & CC	76 sites in USA, Canada, Europe (incl. 11 UK sites, n=10), Australia, New Zealand	Open label 1:1 randomisation

Primary endpoint: SVR12 (HCV RNA <15 IU/mL, 12 weeks after treatment ends)
Secondary endpoints included: SVR4 and SVR24, drug resistance, virologic failure
HRQoL: SF-36, Chronic Liver Disease Questionnaire (CLDQ-HCV), Fatigue Index (FACIT-F) and Work Productivity and Activity Impairment (WPAI)

Clinical evidence for SOF/VEL (2): 2 phase III randomised non-controlled trials

Trial	Int.	Population	Sites	Design
ASTRAL-4	• SOF/VEL 12 weeks • SOF/VEL + R 12 weeks • SOF/VEL 24 weeks	• GT1-6 • TN and TE • Decompensated cirrhosis (Child–Pugh–Turcotte class B)	47 sites in USA	Open-label 1:1:1 randomisation
ASTRAL-5 (ongoing)	• SOF/VEL 12 weeks	• GT 1–6 and HIV • TN and TE • NC & CC	Not reported	Open-label

SVR12 in individual ASTRAL trials (1)

Study	Genotype	Subgroup	SOF/VEL, 12 wks n/N (%) [95% CI]	SOF + R, 24 wks n/N (%) [95% CI]
ASTRAL-3	**GT3**	**All patients** p<0.001	264/277 (95.3) [redacted]	222/275 (80.7) [redacted]
		TN, NC	160/163 (98.2) [redacted]	142/156 (91.0) [redacted]
		TN, CC	40/43 (93.0) [redacted]	33/45 (73.3) [redacted]
		TE, NC	31/34 (91.2) [redacted]	22/31 (71.0) [redacted]
		TE, CC	33/37 (89.2) [redacted]	22/38 (57.9) [redacted]
ASTRAL-2	**GT2**	**All patients** p=0.018	133/134 (99.3) [redacted]	124/132 (93.9) [redacted]
		TN, NC	99/100 (99.0) [redacted]	92/96 (95.8) [redacted]
		TN, CC	15/15 (100.0) [redacted]	14/15 (93.3) [redacted]
		TE, NC	15/15 (100.0) [redacted]	13/16 (81.3) [redacted]
		TE, CC	4/4 (100.0) [redacted]	4/4 (100.0) [redacted]

For results by cirrhotic status only or treatment experience only, see section 4.8.2 company submission

Sources:

- *Results for overall genotype: section 4.7 company submission*
- *Results for subgroups: appendix 5 company submission*

SVR12 in individual ASTRAL trials (2)

Study	Genotype	Subgroup	SOF/VEL, 12 wks n/N (%) [95% CI]
ASTRAL-1 (see appendix 5 company submission for subgroup results for each genotype)	**GT1, GT2, GT4-6**	**All patients** (p<0.001)	618/624 (99.0) [redacted]
		TN	98.8% (n numbers and 95% CI not reported)
		TE	99.5% (n numbers and 95% CI not reported)
		NC	99.0% (n numbers and 95% CI not reported)
		CC	99.2% (n numbers and 95% CI not reported)
	GT1a		206/210 (98.1) [redacted]
	GT1b		117/118 (99.2) [redacted]
	GT2		104/104 (100.0) [redacted]
	GT4		116/116 (100.0) [redacted]
	GT5		34/35 (97.1) [redacted]
	GT6		41/41 (100.0) [redacted]
p<0.001 for SOF/VEL compared with the pre-defined performance goal of 85%			

Sources:

- *Results for all trial patients and each genotype: section 4.7 company submission*
- *Results for subgroups: section 4.8 company submission*

Pooled analysis of ASTRAL-1, -2, -3 (n=1,035)

- High cure rates (SVR12) irrespective of cirrhotic status or prior treatment
  - Overall, 98.1% of people receiving SOF/VEL had SVR12
- 1.3% (n=13) experienced virologic relapse after treatment, of which:
  - none had resistance to SOF
  - 12 had mutations that could confer resistance to VEL; present at baseline in 7 people (presence of baseline mutations not strong predictor of virologic failure)
- No-one experienced on-treatment failure
- 0.7% lost to follow-up, discontinued due to AEs or died

Adverse effects (AEs) of treatment

- No adverse drug reactions specific to SOF/VEL
- Type, incidence and severity of AEs comparable to placebo
- Most common (incidence ≥10%) treatment-emergent AEs:
  - headache, fatigue and nausea (SmPC, pooled data from ASTRAL-1, -2 and -3)
  - [redacted]
- ASTRAL-2 and -3: a lower % of patients in the SOF/VEL group experienced any AE (n=245; 88%) compared with SOF+RBV (n=260; 95%)
  - mainly because of the higher number of AEs known to be associated with RBV (eg fatigue, headache, nausea, insomnia)
- ASTRAL-4 (decompensated cirrhosis): AEs consistent with expected clinical sequelae of decompensated liver disease, or known AEs for ribavirin

Company network meta-analysis (1)

- 1 endpoint analysed: sustained viral response (SVR)
- Reference treatment: Peg-IFN + ribavirin (PR)
- Only 2 networks could be formed: GT1 treatment-naïve and GT3 treatment-naïve
  - For other populations: no studies / disconnected studies / small network
- Results for GT1 treatment-naïve: nearly all treatments showed a statistically significant increase in risk of SVR compared with PR
  - statistically significant increased probability of achieving SVR12 with SOF/VEL (mean risk difference versus PR: 0.71, 95% CrI 0.51 to 0.89)
- Results for GT3 treatment-naïve: no evidence for a statistically significant difference in risk of SVR compared with PR for any treatment in the network
  - non-significant increased probability of achieving SVR12 with SOF/VEL (mean risk difference versus PR: 0.15, 95% CrI −0.01 to 0.42)
- For the populations where an NMA was feasible, the company identified several limitations:
  - NMA did not allow efficacy data to be split by presence/absence of cirrhosis
  - No results for GT1a and GT1b
  - Results for GT3 may have been misleading because 1 trial that was essential to create the network lacked face validity (ELECTRON)
  - Studies in GT3 network were heterogeneous for METAVIR fibrosis score (a known treatment effect modifier)

Company network meta-analysis (2)

- Because of the limitations identified, and the fact that NMA networks could not be formed for all the subgroups of interest, the company did not use the results of the NMA in its model.
- For its model, the company extracted data from individual trials identified in a systematic literature review, **except** for PR in the GT2 treatment-naïve subgroup (see below)
  - Data for SOF/VEL were sourced from ASTRAL-3 for GT3, ASTRAL-2 for GT2, and ASTRAL 1 for GT1 and GT4-6.
  - See table 39 on page 131 company submission for sources of SVR rates for each of the comparators (stratified by genotype, treatment history and presence/absence of cirrhosis).
- The company estimated SVR rates for PR in the GT2 treatment-naïve subgroups using a Bucher indirect treatment comparison. The company used data from the FISSION trial of PR versus SOF+RBV, and the ASTRAL-2 trial of SOF/VEL versus SOF+RBV. It used risk differences in the model because it considered that the odds ratios were not credible:
  - SVR in GT2 TN NC: positive risk difference for SOF/VEL of 18.41% versus PR → SVR of 99% for SOF/VEL and a derived rate of 80.59% for PR
  - SVR in GT2 TN CC: positive risk difference for SOF/VEL of 28.46% versus PR → SVR of 100% for SOF/VEL and a derived rate of 71.54% for PR
- The SVR rates used in the company model are presented in the following 3 slides

SVR12 rates, % (1)
(clinical data used in company model)

GT	1				1a				1b			
TE/TN	TN		TE		TN		TE		TN		TE	
Cirrhotic?	NC	CC	NC	CC	NC	CC	NC	CC	NC	CC	NC	CC
SOF/VEL	98.4	98.5	98.4	98.5	97.5	100	97.5	100	100	95.8	100	95.8
SOF+PR	91.7	80.8	74.0	74.0	91.7	80.8	74.0	74.0	91.7	80.8	74.0	74.0
DCV+SOF +R	-	100	-	100	-	100	-	98.5	-	100	-	98.5
DCV+SOF	100	-	100	-	100	-	100	-	100	-	100	-
PR	43.6	23.6	17.6	10.0	43.6	23.6	17.6	10.0	43.6	23.6	17.6	10.0
LDV/SOF	94.0	94.1	95.4	86.4	94.0	94.1	95.4	86.4	94.0	94.1	95.4	86.4
OPR+D±R	-	95.4	-	-	97.0	92.9	96.0	95.4	99.0	100.0	100	97.8
SMV+PR	82.0	60.4	80.1	74.4	82.0	60.4	80.1	74.4	82.0	60.4	80.1	74.4

SVR for GT1, 1a and 1b is by cirrhosis only - no distinction between subgroups according to prior treatment
Source: section 5.6.1 company submission: table 98 (page 236) and table 105 (page 244)

SVR12 rates, % (2)
(clinical data used in company model)

GT	2				3				4			
TE/TN	TN		TE		TN		TE		TN		TE	
Cirrhotic?	NC	CC	NC	CC	NC	CC	NC	CC	NC	CC	NC	CC
SOF/VEL	99.0	100	100	100	98.2	93.0	91.2	89.2	100	100	100	100
SOF+R	95.8	93.3	81.3	100	90.4	73.3	71.0	57.9	-	-	-	-
SOF+PR	-	-	-	-	95.8	91.3	94.2	85.7	100	50	100	50
DCV+SOF +R	-	-	-	-	-	57.9	-	69.2	-	-	-	-
DCV+SOF	-	-	-	-	77.8	-	71.4	-	-	-	-	-
PR	80.6	71.5	35	35	71.2	29.7	35.0	35.0	45.0	25.0	45	25
LDV/SOF	-	-	-	-	-	-	-	-	95.2	100	84.6	100
OPR+D+R	-	-	-	-	-	-	-	-	100	100	100	100
SMV+PR	-	-	-	-	-	-	-	-	84.4	66.7	63.6	46.4
DCV+PR					-	-	-	-	81.2	77.8	81.2	77.8

Source: section 5.6.1 company submission: tables 90, 94, 109, 113, 117 and 121 (pages 249-256)

SVR12 rates, % (3)
(clinical data used in company model)

GT	5				6			
TE/TN	TN		TE		TN		TE	
Cirrhotic?	NC	CC	NC	CC	NC	CC	NC	CC
SOF/VEL	96.6	100	100	100	100	100	100	100
SOF+PR	100	50	100	50	100	50	100	50
PR	45.0	25.0	-	-	45.0	25.0	-	-
LDV/SOF	94.4	100	100	83.3	96.0	96.0	96.0	96.0

SVR in decompensated cirrhosis:

- SOF/VEL + R: 94.3%
- LDV/SOF + R: 86.4%

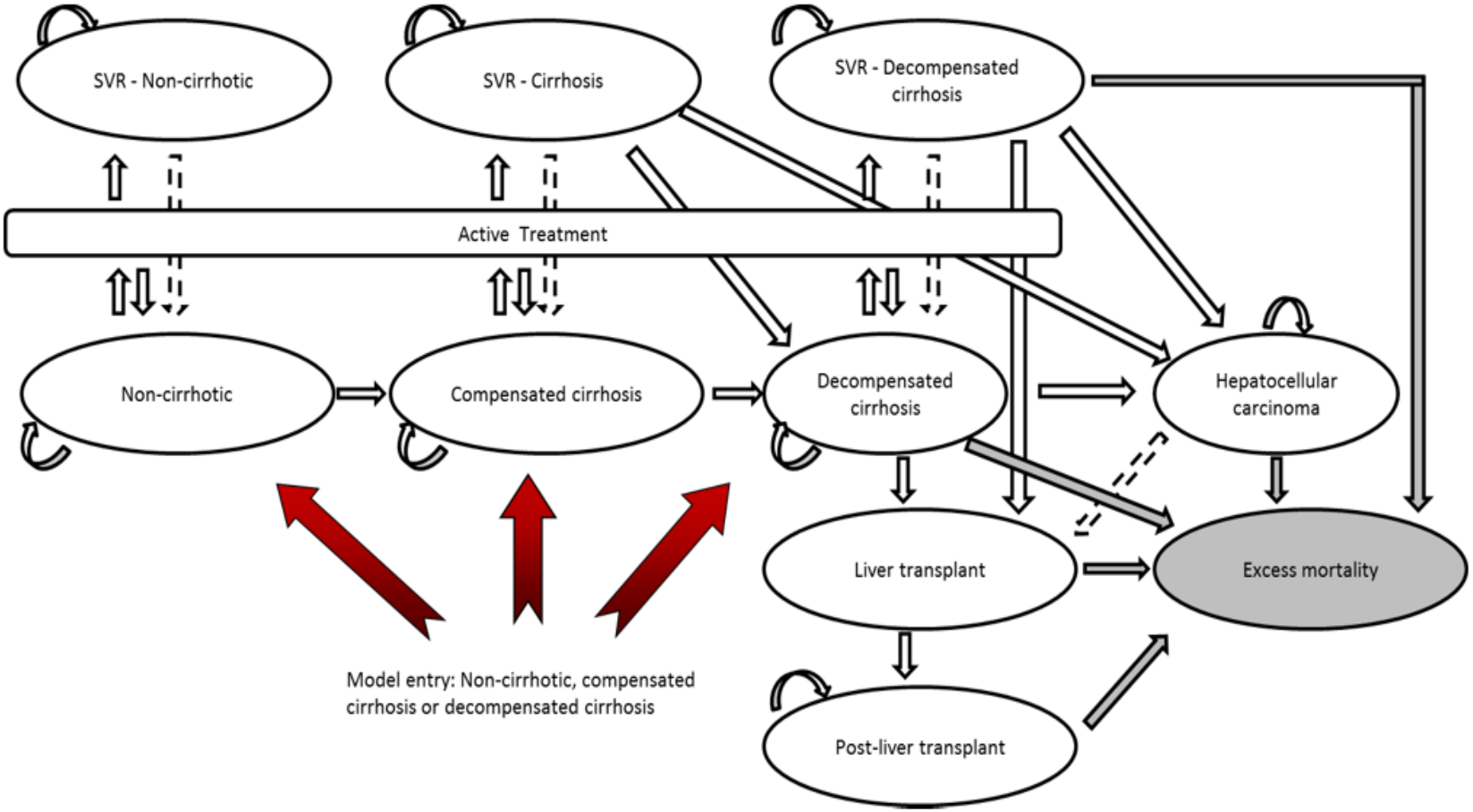
Source: section 5.6.1 company submission: tables 117, 121 and 125 (pages 253-259)

Cost-effectiveness evidence

company submission chapter 5

Company's 10-state Markov model

Lifetime horizon up to 100 years, starting age of 40 or 45 years, 79kg weight
2 week cycles for 72 weeks, one 24-week cycle, yearly cycles thereafter



Dashed arrows are only considered in sensitivity analyses
Connecting arrow between the compensated cirrhosis and hepatocellular carcinoma health states not shown (see company response to clarification question C4)
All patients experience a background mortality risk equivalent to general population, except in active treatment phase where there is no risk

Company model inputs & assumptions:
similarities to previous Hep C NICE appraisals (1)

- People with mild and moderate chronic hepatitis C (METAVIR score F0-F3) grouped within a single health state (“non-cirrhotic”)
  - In TA330 (SOF) and TA363 (LDV/SOF) committee concluded it appropriate to group mild and moderate hepatitis C into 1 state, because it is consistent with how people are diagnosed in current practice, using less invasive diagnostic tests than historically
  - NB this grouping meant there was no opportunity for spontaneous SVR in mild patients (a scenario modelled in previous appraisals)
  - Other models separated health states according to METAVIR score or mild/moderate
- Decompensated cirrhosis covers multiple possible health states (eg ascites, hepatic encephalopathy and hepatorenal syndrome) to allow for several simultaneous complications
- Utility estimates
  - Fibrosis health state utility values taken from Wright et al., 2006
  - SVR-related utility increment of 0.04 taken from Vera-Llonch et al., 2013
    - Consistent with TA330 and TA363 (other appraisals used 0.05 from Wright et al. 2006)
    - In TA365, the committee concluded that the SVR-related utility value would lie between the trial estimate and the estimate from Wright et al., 2006
  - Treatment-specific utility increments/decrements applied (consistent with TA330 and TA363)
  - Utility decrements to adjust for the impact of adverse events

Company model inputs & assumptions:
similarities to previous Hep C NICE appraisals (2)

- SVR, treatment duration and adverse events taken directly from individual comparator studies
- Non-treatment specific transition probabilities of moving to more severe health states were taken from a variety of different studies, and are consistent with previous appraisals, **except**
  - non-cirrhotic to the compensated cirrhosis health state (see next slide)
  - compensated or decompensated cirrhosis to hepatocellular carcinoma (see next slide)
- Patients with HIV co-infection are treated the same as those with HCV mono-infection and have the same outcome
  - Company states this is a conservative assumption: disease would progress more quickly in people with co-infection than in mono-infection if untreated; therefore any given treatment would be more cost-effective when treating co-infection compared with mono-infection
- Re-infection after achieving SVR not accounted for in base case (scenario only)
  - Re-infection resulted in restarting treatment in the patient's initial health state (that is, assuming that liver damage caused by HCV is not fully reversible)
- Broadly the same sources and values for costs as in TA330 and TA363 because the company's systemic literature review did not identify any new data (but inflated to 2014/15)

Company model inputs & assumptions:
differences from previous Hep C NICE appraisals

- Transition probabilities for the non-cirrhotic state to the compensated cirrhosis health state:
  - based on Kanwal 2014
  - assumed to be faster in GT3
- Transition probabilities from compensated or decompensated cirrhosis to hepatocellular carcinoma
  - based on Cardoso et al. 2010
  - previous appraisals used Fattovich et al. 1997 and Cardoso et al. 2010
- Short 2-week cycles initially, to allow for varied treatment durations of comparators
  - Most other models start with yearly cycles, some used monthly, TA253 used weekly cycles
- Patients do not die of non-hepatitis C causes during the treatment period (consistent with TA363)
- Previous models have included boceprevir and telaprevir
- GT4 data from trials of SOF/VEL were used for GT4 patients in model
  - in previous appraisals, GT1a or 1b outcome data were used as a proxy for GT4 because sample size for GT4 too small

Company model inputs:
transition probabilities (TPs) (1)

TP from the non-cirrhotic state to the compensated cirrhosis health state

- In TA363 (LDV/SOF) – the ERG said details were insufficient to critique robustness of approach for how this TP was calculated
- Company noted that this transition is important because genotype affects the rate of disease progression, with GT3 being linked to faster progression and increased risk of hepatocellular carcinoma compared with other genotypes
- The company did a targeted literature review, with a focus on GT3
  - Identified 11 studies; selected Kanwal et al. 2014 (n=8337) study of US veterans (provided data for all genotypes)
  - Kanwal et al. showed more rapid progression in GT3 than other GTs, but the TP from non-cirrhotic to compensated cirrhosis was conservative compared with other studies, and validated by experts as generalisable to UK
  - The company model therefore assumed that progression from non-cirrhotic to compensated cirrhosis was faster in GT3; different to models submitted for previous appraisals of SOF

TP from compensated or decompensated cirrhosis to hepatocellular carcinoma

- In TA363 (LDV/SOF) the committee concluded that this TP lies somewhere in between 0.014 (Fattovich et al. 1997) and 0.0631 (Cardoso et al. 2010); most plausible ICERs used both
- In the current submission, the company used 0.631 from Cardoso et al.

Company model inputs:
transition probabilities (TPs) (2)

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	Calculated
	HCC	0.0631	Cardoso et al 2010	Calculated
CCSVR	**DCC**	0.0064	Cardoso et al 2010	Calculated
	HCC	0.0128	Cardoso et al 2010	Calculated
DCC	**HCC**	0.0631	Cardoso et al 2010	Calculated
	Liver transplant	0.022	Siebert 2005	
	Death	0.24	EAP data (EASL 2016)	
DCC SVR	**HCC**	0.0631	Assumption	Assumed same as TP from DCC without SVR
	Liver transplant	0.022	Assumption	Assumed same as TP from DCC without SVR
	Death	0.049	EAP data (EASL 2016)	
HCC	**Death**	0.4300	Fattovich et al, 1997	Used in TA106
Liver transplant	**Death, Yr1**	0.2100	Bennett et al 1997	Used in TA106
Cardoso included patients stage at F3 and F4 and DCC was defined as several liver-related complications *Source: table 81 company submission*				

Company model inputs:
health-state utilities

Health state	Utility
Baseline: non-cirrhotic	0.75 (Wright et al. 2006)
Baseline: compensated cirrhosis	0.55 (Wright et al. 2006)
Baseline: decompensated cirrhosis, hepatocellular carcinoma and liver transplant	0.45 (Wright et al. 2006)
Post liver transplant	0.47 (Wright et al. 2006)
Source: table 82 company submission	

- Utility increment after SVR: 0.04
  - From Vera-Llonch et al 2013 (US EQ-5D tariff); consistent with TA330 & TA363
  - Company noted that, although Wright et al. uses a UK EQ-5D tariff, Vera-Llonch et al. was the most recent source with the least uncertainty
- No time-dependent utility change within health states
- Adverse events reduce utility
- Once treatment stops: no quality of life, adverse event (AE) or cost implications persist
  - Patients return to the utility value relevant to the post treatment health state they are in, and future AEs and their associated costs cannot occur

Company model inputs:
treatment-specific utilities

- Treatment-specific utility decrements
  - Applies for regimens containing interferon or ribavirin
  - Associated with mood and psychiatric disturbance, nervous system effects, diarrhoea and nausea, generalised systemic effects (eg reduced appetite), asthenia, itch and inflammatory skin disorders and pain (muscular and joint)
    - For ribavirin-containing regimens: −1.00% to −6.88%
    - For interferon-containing regimens: −14.27% to −14.77%
- Treatment-specific utility increments
  - Applied for direct-acting antivirals because they are not associated with the adverse effects of interferon and ribavirin AND are improve quality of life due to rapid early suppression of the virus
    - 4.43% (all direct-acting antivirals)
- Data sourced from trials where possible but some assumptions made
  - eg on-treatment utility values for LDV/SOF (SF-36 data converted to SF-6D) were applied to SOF/VEL, due to lack of evidence from ASTRAL trials
- The company reported that the impact of removing treatment-specific utilities is negligible (see response to clarification question C12)

Application of price discounts

- 2 comparators are recommended by NICE with confidential price discounts agreed with the Commercial Medicines Unit (discounted prices not known by the company):
  - ombitasvir/paritaprevir/ritonavir (OPR) (TA365)
  - daclatasvir (DCV) (TA364)
- Because the discounts are confidential, cost-effectiveness analyses in the company submission and ERG report which contain OPR or DCV as comparators use the list prices for OPR, DCV and SOF/VEL.
  - *Note: these results are not reflective of the true cost effectiveness of SOF/VEL and are not presented in this premeeting briefing*
- In its confidential appendix, the ERG reproduced the company base case and its own base case using the confidential discounted prices for OPR, DCV **and** SOF/VEL.
- The results presented in this premeeting briefing document reflect discounted prices of the intervention and comparators. Exact ICERs cannot be published for analyses which contain OPR or DCV as comparators, to protect the confidentiality of the discounts.
- The company presented fully incremental results and the ERG presented only pairwise comparisons (that is, the ICER for SOF/VEL compared with each comparator individually). Therefore, for analyses which contain OPR or DCV as comparators, fully incremental results with the discounted prices for OPR and DCV are not available (only pairwise comparisons using discounted prices are available). Fully incremental analyses using list prices are presented in the company submission, but not in this premeeting briefing document because they do no reflect the true cost effectiveness of SOF/VEL.

Cost-effectiveness results based on company's base case assumptions (1)

fully incremental results with discounted price for SOF/VEL

The ICER for SOF/VEL compared with the next non-dominated comparator was between

- £2,379 and £32,595 for **GT2** (TN NC, TN CC, TE NC and TE CC; including IFN-ineligible)
  - SOF/VEL had an ICER of £32,595 compared with PR in GT2 TN NC
  - Excluding this population, the maximum ICER was £12,384
- £3,893 and £15,199 for **GT3** (TN NC, TN CC, TE NC and TE CC; not including IFN-ineligible)
- £2,395 and £2,462 for **GT4** (TN CC and TE CC)
  - The results for GT4 do not include OPR because the company did not include OPR in the GT4 cirrhotic subgroup (NICE TA365 recommends OPR for all GT4 subgroups)
- £2,395 and £6,229 for **GT5 and GT6** (TN NC, TN CC, TE NC and TE CC)

In DCC, SOF/VEL plus ribavirin dominated LDV/SOF plus ribavirin

Note:

- Fully incremental results are not presented for subgroups for whom OPR or DCV are comparators, because fully incremental results **with the discounted prices for OPR and DCV** are not available (see previous slide). Pairwise results for all populations, using the company's base case assumptions and including relevant price discounts are summarised on the next slide.

Cost-effectiveness results based on company's base case assumptions (2)

pairwise results with discounted prices for SOF/VEL, OPR & DCV

Summary

At a willingness-to-pay threshold of £20,000/QALY, SOF/VEL was cost effective compared with all treatments in all populations **except** compared with peginterferon and ribavirin (PR) for treating GT2 treatment-naïve non-cirrhotic CHC in people eligible for interferons (ICER £32,595 per QALY gained).

[redacted]

- [redacted]
- [redacted]
- [redacted]

GT1

- SOF/VEL was cost effective compared with no treatment or PR in all populations (ICERs ranged from £1,144–£4,996/QALY)
- SOF/VEL [redacted]
  - compared with LDV/SOF in GT1 TN NC, where SOF/VEL had an ICER of £8,288/QALY
- [redacted]
- *These results include comparisons with DCV/SOF/RBV 24w, which the company did not include but the ERG did (using results for DCV/SOF 12w as a proxy)*

Cost-effectiveness results based on company's base case assumptions (3)

pairwise results with discounted prices for SOF/VEL, OPR & DCV

GT2

- SOF/VEL was cost effective compared with no treatment or PR in all populations (ICERs ranged from £2,424–£12,384/QALY) **except** compared with PR in TN NC (ICER £32,595/QALY)
- [redacted]

GT3

- SOF/VEL was cost effective compared with no treatment or PR in all populations (ICERs ranged from £2,855–£15,199/QALY)
- [redacted]
- [redacted]

GT4

- SOF/VEL was cost effective compared with no treatment or PR in all populations (ICERs ranged from £1,405–£6,232/QALY)
- [redacted]
  - BUT company did not include regimens containing daclatasvir or simeprevir

Cost-effectiveness results based on company's base case assumptions (4)

pairwise results with discounted prices for SOF/VEL, OPR & DCV

GT5/6

- SOF/VEL was cost effective compared with no treatment or PR in all populations (ICERs ranged from £1,405–£6,229/QALY)
- [redacted]

DCC

- SOF/VEL dominated LDV/SOF/RBV in both subpopulations (treatment-naïve and treatment-experienced)

Company's deterministic and probabilistic sensitivity analyses

Deterministic sensitivity analyses (DSA)

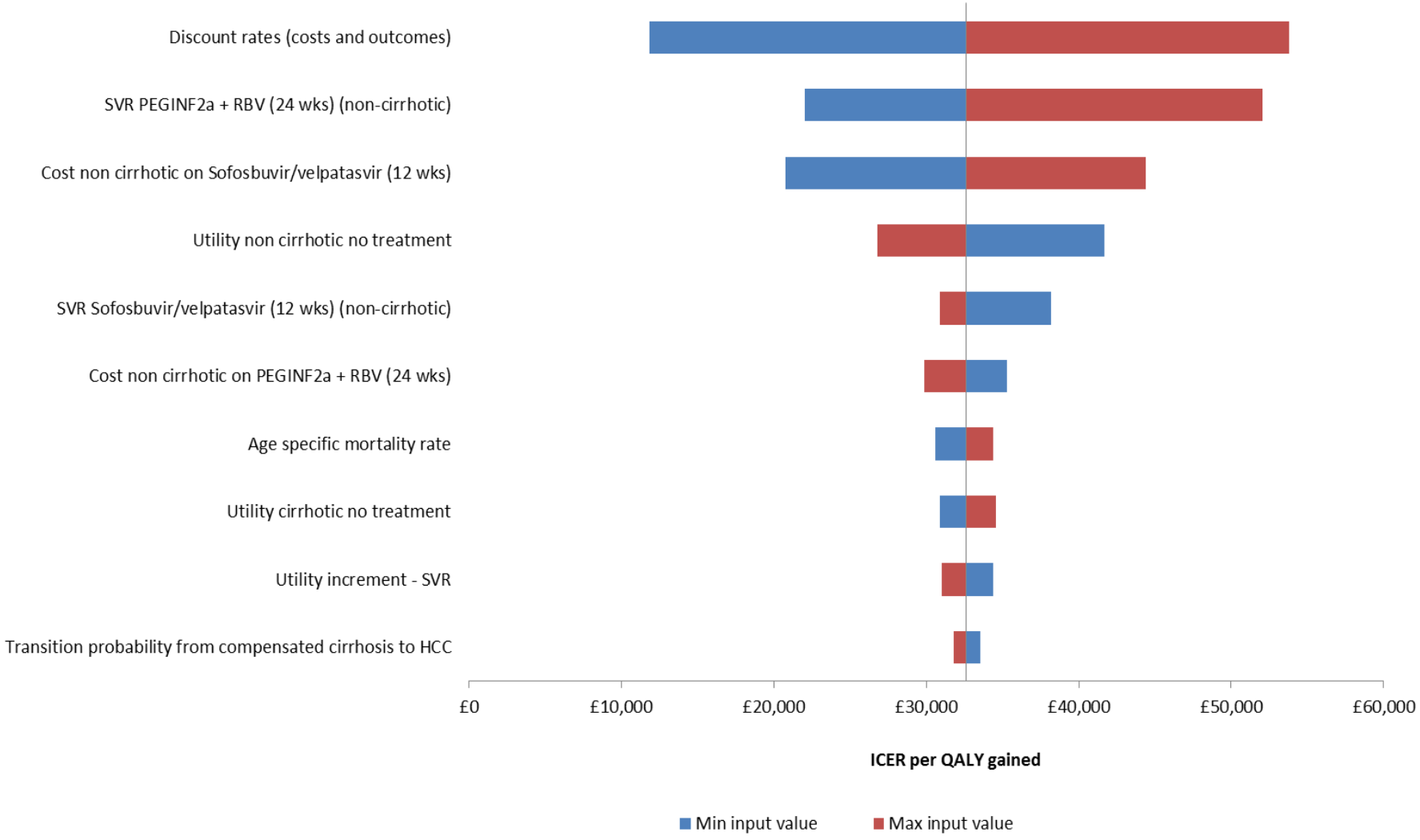
- Company presented results of DSA only for treatment-naïve non-cirrhotic subgroups for GT1-GT4
- The ICER was most sensitive (ICER range >£10,000) to following variables:
  - Treatment costs (for LDV/SOF and SOF/VEL)
  - Discount rates (costs and outcomes)
  - SVR probability (for LDV/SOF, PR and SOF/VEL)
  - Utility non cirrhotic (baseline)
- The ICER was not sensitive to including a risk of re-infection after SVR

Probabilistic sensitivity analyses (PSA)

- The probabilistic ICERs appeared similar to the deterministic ICERs
- The probability that SOF/VEL is cost effective ranged from 18%-93% for a threshold value of £20,000 and 23%-95% for a threshold value of £30,000
  - *Note: this includes analyses that do not reflect approved confidential discounts*
- For only the analyses with discounted prices: probability SOF/VEL is cost effective ranged from 42%-93% for a threshold value of £20,000 and 52%-95% for a threshold value of £30,000
  - *Note: this excludes the following populations: GT1a overall TN NC, TN CC, TE NC, TE CC; GT1b overall TN NC, TN CC, TE NC, TE CC; GT 1 overall TN NC, TN CC, TE NC, TE CC; GT3 IFN-ineligible TN NC, TN CC, TE NC, TE CC; GT4 overall TN NC, TE NC*

Company's DSA:

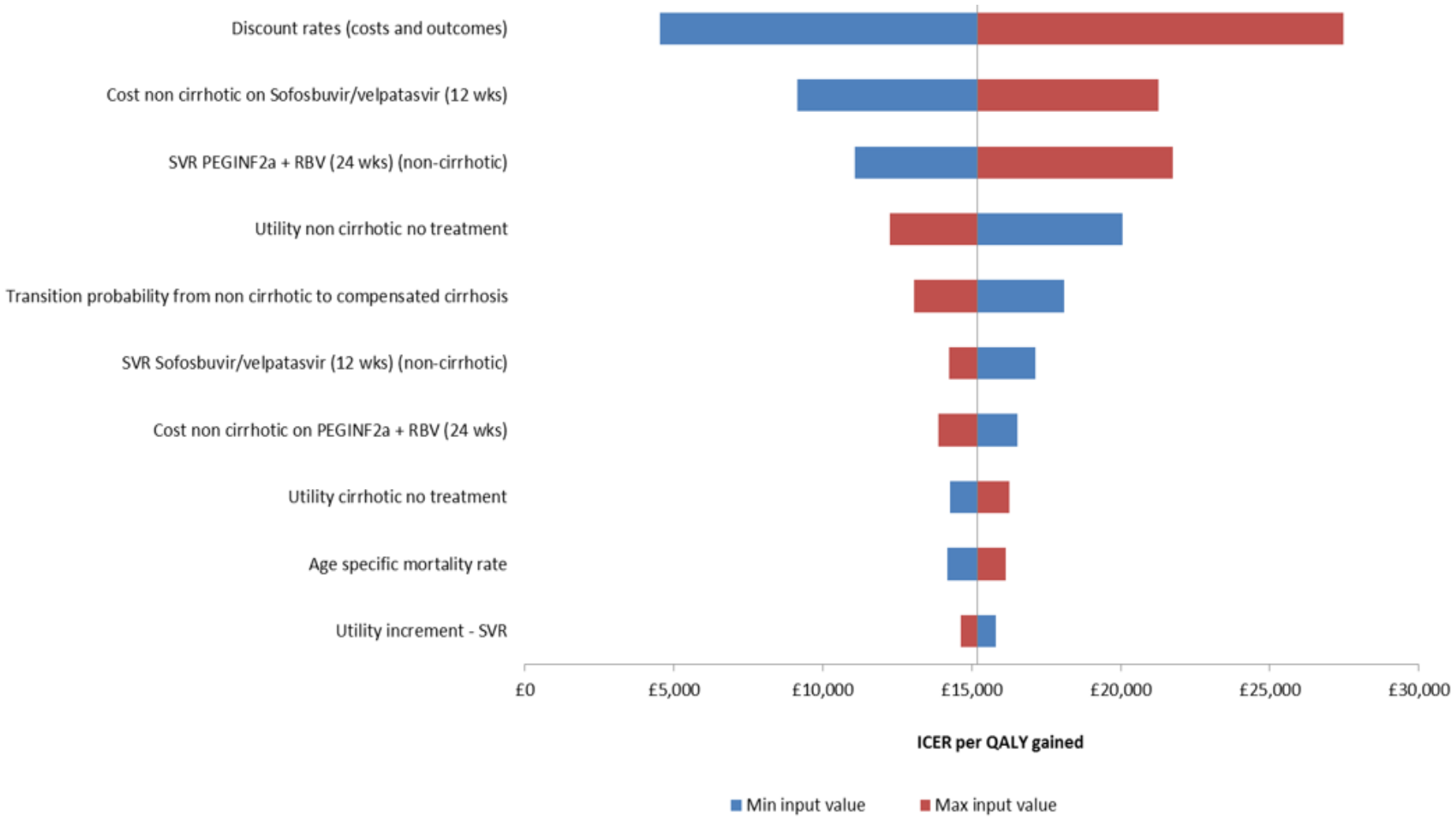
tornado diagram for GT2 TN NC (figure 62 company submission)



pre-meeting briefing document

Company's DSA:

tornado diagrams for GT3 TN NC (figure 60 company submission)



pre-meeting briefing document

Company's scenario analyses

- The company modelled some of the comparators in the scope as scenarios only
  - DCV+SOF+R 24w in GT1 and GT4 IFN-ineligible cirrhotic patients
  - DCV+SOF±R 12w in GT4 patients
  - DCV+PR in GT4 patients
  - SMV+PR in GT4 patients
  - OPR in GT4 cirrhotic patients

- The results for some of these are captured in the summaries in slides 32 and 33:
  - DCV+SOF+R 24w in GT1 IFN-ineligible cirrhotic patients
  - OPR in GT4 cirrhotic patients

- The company did not perform any additional scenario analyses

Full results from scenario analyses are presented in section 5.8.3 of the company submission (page 354-67)

ERG critique

Summary of ERG critique (1)

Generally, SOF/VEL trials were well conducted. Higher risk of bias for ASTRAL-3 and 2 because they were open-label studies. In addition, in ASTRAL-3 there were more dropouts in the comparator arm (n=21) than in the intervention arm (n=2).

The ERG noted similar issues to previous TA models that have already been highlighted but accepted by the appraisal committee

- Cost-effectiveness results were at risk of bias because SVR, discontinuation rates and AEs were taken directly from individual trials (see slide 42). Not adjusted for in ERG's exploratory analyses.
- Issues relating to calculation of utility values and increments:
  - Preferable to use SOF/VEL trial data to derive health state utility values and the SVR utility increment, rather than published literature. Not adjusted for in ERG's analyses.
  - Wright et al. 2006 not the most appropriate source for utilities because data collected between 1996-2002 (not reflective of current practice). Not adjusted for in ERG's analyses.
  - Estimates of on-treatment utility increments and decrements were not fully justified (and sources not provided). However, the ERG agreed that the direction of effect of the different treatments is accurately reflected and that removing these increments does not impact the cost-effectiveness results (response to clarification questions C12b).
- The company model oversimplified the disease by:
  - Grouping mild and moderate cirrhosis into 1 health state. Not changed in ERG's analyses.
  - Not including re-infection or treatment failure. This favours all active treatments. The ERG's analyses allowed for re-infection.

Summary of ERG critique (2)

The ERG had concerns about some differences from previously accepted TA models:

- The company did not systematically identify sources for all transition probabilities (see slide 43).
  - The ERG's exploratory analyses corrected errors in the transition probabilities but the ERG could not systemically identify alternative sources for transition probabilities.
- Published literature (Wright et al. 2006) does not support the application of a utility increment for people with decompensated cirrhosis who achieved an SVR.
  - The ERG's exploratory analyses did not include this increment.

Additional ERG comments:

- The company's utility value for the 'non-cirrhotic' health state was based on a weighted average of mild (83%) and moderate (17%) CHC patients. The ERG was concerned that these proportions were not underpinned with evidence and was not able to assess the validity of these figures.
- The company's model lacked face/internal validity (see slide 44).
- The company's probabilistic sensitivity analyses were potentially biased and difficult to interpret.
- The ERG could not calculate results for all comparators because the company had not included them in its executable model, and for some comparators it was forced to make assumptions in order to include them (for example, assuming the results for DCV+SOF+RBV are equal to DCV+SOF for patients with GT1 CHV and compensated cirrhosis).

Detailed ERG critique:
using individual study data for SVR rates in model

The ERG agreed that the NMA results were not suitable for use in the economic analysis. However, the ERG stated 3 concerns about the company's approach to using individual study data:

1. The company selected 1 source for each intervention in each population → risk of bias
   - the ERG considered that the company's choice of study was often arbitrary
   - selecting results from a single arm of a study means that results are open to the risks of bias associated with observational studies
2. The company selected SVR rates from RCTs identified in its original literature search. The ERG considered that, because data were taken from individual study arms, all types of study design (eg uncontrolled studies, non-randomised) are valid for inclusion and should have been included.
3. Some studies presented multiple SVR rates; the ERG considered that the company's choice of 1 SVR rate from each study was arbitrary.

The company justified its sources in response to clarification question B2a, and showed that using an alternative source did not change the cost-effectiveness results. The ERG considered the company's justifications for choosing each SVR to be valid, but suggested:

- equally valid justifications could have been provided for alternative sources
- using multiple alternative sources across different interventions may have changed the results
- the company could have listed the available options and calculated a mean.

The ERG questioned whether differences in SVR rates between comparators are true differences or driven by differences between studies (eg difference in study population). It noted that the company's DSA showed the model was sensitive to SVR rates (see slides 35-37)

Detailed ERG critique:
transition probabilities (TPs)

The ERG considered that the company's assumption of faster progression of liver fibrosis in GT3 was supported, but had concerns about the company's approach to estimating the GT3-specific TP from the non-cirrhotic to the compensated cirrhotic health state. The ERG considered that:

- The company's targeted literature search to identify TPs from the non-cirrhotic to the compensated cirrhotic health state for the GT3 population was inadequate.
- All TPs in all populations should have been selected from the results of systematic searches.

The ERG also had concerns about the other treatment-independent TPs:

- The company did not justify its assumption that all other TPs were independent of prior treatment and genotype.
- The company did not justify the TPs from the compensated and decompensated cirrhosis health states (with and without SVR) and the ERG could not find them in the source provided.
  - Particularly the probability of death from the decompensated cirrhosis health states with and without SVR (0.049 and 0.240 respectively); the ERG noted that previous appraisals did not model an impact of SVR status on the probability of death from decompensated cirrhosis.
- It was inappropriate for the company to assume that data from patients with several liver-related complications is equivalent to patients with decompensated cirrhosis.
- The ERG identified calculation errors in the transition probabilities

The ERG **does not consider these to be priority issues** because these transition probabilities were treatment independent, **except for the SVR status-dependent TPs** as these might drive the differences between the different treatments

Detailed ERG critique:
model lacked face/internal validity

The ERG considered that the following assumptions oversimplified the model and lacked face validity, but did not adjust for them in its exploratory analyses because it considered that the company's approach was conservative (that is, underestimated the effectiveness of active treatments, including SOF/VEL):

- assuming a year with 48 weeks
- incorporating a period without any disease progression and mortality
- not adjusting the liver transplant tunnel for shorter cycle lengths, meaning that the impact of a liver transplant on costs and QALYs was underestimated for liver transplants that occur during the first 38 cycles (when cycle lengths were shorter).

The ERG was concerned that the total health benefits of more effective treatments with higher SVR rates may have been underestimated, because the model could not incorporate effects on the population infection rate.

The ERG considered that the results of the company's probabilistic analyses were potentially biased and difficult to interpret because:

- The company model was unable to consider multiple comparators simultaneously in the probabilistic analyses (which is methodologically incorrect)
- The company did not include all comparators in the scope in its base case, and therefore might have overestimated the probabilities of being cost effective.

ERG base case: assumptions

The ERG created its own base case in which it made the following changes:

- Corrected errors in transition probabilities calculated by the company.
- Incorporated an annual reinfection probability of 2.4% (standard error: 1.4%) in the non-cirrhotic, compensated cirrhosis and decompensated cirrhosis health states (based on a systematic review and meta-analysis by Aspinall et al. 2013).
- Removed the utility increment for achieving SVR from decompensated cirrhosis health state.

For the subgroups with GT1, the ERG presented the results for the combined GT1 group (instead of presenting separate results for GT1a and GT1b).

- The ERG suggested that the difference in response between GT1a and GT1b is small and is unlikely to be a major issue from a clinical perspective.
- The only difference in comparators for GT1a and GT1b is OPR, which the ERG handled as follows:
  - data for OPR+D (without RBV) was retrieved from GT1b (not available for GT1a)
  - data for OPR+D+RBV retrieved from GT1a.
- The ERG justified this because all treatment independent transition probabilities are equal for GT1, GT1a and GT1b.

ERG base case: pairwise results (1)
using discounted prices for SOF/VEL, OPR & DCV

The ERG presented pairwise comparisons of SOF/VEL with each comparator.

At a willingness-to-pay threshold of £20,000/QALY, SOF/VEL was cost effective compared with all treatments in all populations **except** compared with peginterferon and ribavirin (PR) for treating:

- GT2 treatment-naïve non-cirrhotic CHC in people eligible for IFN (ICER £44,545/QALY)
- GT3 treatment-naïve non-cirrhotic CHC in people eligible for IFN (ICER £21,479/QALY)

GT1

- SOF/VEL was cost effective compared with no treatment or PR in all GT1 populations (ICERs ranged from £2,897–£8,273/QALY)
- SOF/VEL [redacted]
  - LDV/SOF in GT1 TN NC, where SOF/VEL had an ICER of £12,150/QALY
- [redacted]
- *Note that the ERG used results for DCV/SOF (12w) as a proxy for DCV/SOF/RBV 24w for people with cirrhosis*

GT2

- SOF/VEL was cost effective compared with no treatment or PR in all populations (ICERs ranged from £4,419–£17,947/QALY) **except** compared with PR in TN NC (ICER £44,545/QALY)
- [redacted]

ERG base case: pairwise results (2)

using discounted prices for SOF/VEL, OPR & DCV

GT3

- SOF/VEL was cost effective compared with no treatment or PR in all populations (ICERs ranged from £5,107–£7,694/QALY) **except** compared with PR in TN NC (ICER £21,47/QALY)
- [redacted]
- [redacted]

GT4

- SOF/VEL was cost effective compared with no treatment or PR in all populations (ICERs ranged from £3,265–£9,689/QALY)
- [redacted]
- *Note that regimens containing daclatasvir or simeprevir were not included in these analyses (see next slide)*

GT5/6

- SOF/VEL was cost effective compared with no treatment or PR in all populations (ICERs ranged from £3,319–£9,689/QALY)
- [redacted]

DCC

- SOF/VEL dominated LDV/SOF/RBV in both subpopulations (treatment-naïve and treatment-experienced)

ERG base case: limitations

- The ERG could not calculate results for all comparators because the company had not included them in its executable model. The ERG was not able to include in its base case:
  - DCV+SOF+R 24w in GT4 IFN-ineligible cirrhotic (dominated by SOF/VEL at list prices)
  - DCV+SOF±R 12w in GT4 patients (dominated by SOF/VEL, or more costly for the same QALY gains, at list prices)
  - DCV+PR in GT4 patients
    - The ERG was concerned that it could not calculate results for this comparison (neither using its own base case nor when applying discounts to the company model), because the company analysis using list prices resulted in an ICER for SOF/VEL substantially >£30,000/QALY in treatment-naïve patients with GT4 CHC, and no cirrhosis
  - SMV+PR in GT4 patients (dominated by SOF/VEL at list prices, except in TN CC where SOF/VEL was dominated)
- In order for the ERG to calculate results for the comparison with DCV+SOF+RBV in patients with GT1 and compensated cirrhosis (which the company did not include in its model) the ERG assumed that the results for DCV+SOF+RBV were equal to DCV+SOF.
- The ERG stated that its results should be interpreted with caution, because the treatment effectiveness parameters were based on questionable assumptions/methods (that is, arbitrary selection of single SVR, discontinuation and AE rates from single study arms for each treatment)
- The ERG did not perform probabilistic analyses because, according to the ERG, the economic model submitted by the company was unable to consider multiple comparators simultaneously in the probabilistic analyses (which is methodologically incorrect).

Equality issues

The following potential equality issues were raised:

- A higher prevalence of disease or specific genotypes (genotypes 3 and 4) in people who inject drugs and among minority ethnic groups
  - From company and professional organisations

Innovation

- First pan-genotypic, all-oral, interferon- and ribavirin-free regimen
  - Particular unmet need for interferon-free treatment in treatment-experienced people with GT3 and cirrhosis
- For all adult patients, including those with compensated cirrhosis
  - by adding ribavirin, can treat decompensated cirrhosis
- The only ribavirin-free treatment for GT 2/3
- >94% SVR12 rates across all genotypes and subgroups
- Meets a need identified as important by NHS
  - NHS Outcomes Framework commitment to reducing mortality due to liver disease in people under 75 years of age
- Benefits not captured in QALY:
  - reduction in onward transmission of HCV due to effective treatment
  - reversal of liver fibrosis once cured

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Sofosbuvir-velpatasvir for treating chronic hepatitis C

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of the combination of sofosbuvir and velpatasvir within its marketing authorisation for treating chronic hepatitis C.

Background

The hepatitis C virus (HCV) causes inflammation of the liver and affects the liver's ability to function. HCV is a blood-borne virus, meaning that it is spread by exposure to infected blood. Contaminated needles used to inject drugs are currently the most common route of transmission. Symptoms of chronic hepatitis C are typically mild and non-specific, including fatigue, flu-like symptoms, anorexia, depression, sleep disturbance, pain, itching and nausea. Often, people with hepatitis C do not have any symptoms, and 15 to 20% of infected people naturally clear their infections within 6 months.[1] However, most people develop chronic hepatitis which can be life-long.

Chronic hepatitis C is categorised according to the extent of liver damage, as mild, moderate, or severe (where severe refers to cirrhosis). Cirrhosis is severe scarring that has spread throughout the liver. About 20% of people with chronic hepatitis C develop cirrhosis;[2] the time for progression to cirrhosis varies, but it takes up to 40 years (20 years on average).[1] Cirrhosis can progress to become 'decompensated', which means the remaining liver can no longer compensate for the loss of function. A small percentage of people with chronic hepatitis and cirrhosis also develop hepatocellular carcinoma. Liver transplantation may be needed for people with decompensated cirrhosis or hepatocellular carcinoma.

The true prevalence of HCV infection is difficult to establish and likely to be underestimated because many people do not have symptoms and more than half of people with chronic hepatitis C are unaware of their infection.[3] There are 6 major genotypes and several subtypes of HCV; the prevalence of each varies geographically. Recent estimates (2012) suggest that around 160,000 people have been diagnosed with chronic hepatitis C in England, and that approximately 90% of these people are infected with genotype 1 or 3.[4]

The aim of treatment is to cure the HCV infection and prevent liver disease progression, hepatocellular carcinoma development, and HCV transmission. The HCV genotype influences response to treatment and therefore the treatment decisions. For those with mild hepatitis C, a 'watchful waiting'

approach may be agreed between the patient and clinician on an individual basis.

NICE guidance on hepatitis C (NICE technology appraisal guidance 75, 106, 200, 252, 253, 330, 331, 363, 364 and 365) recommends:

- combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b for people with chronic hepatitis C regardless of disease severity, genotype or treatment experience.
- monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended for people who are unable to tolerate ribavirin or for whom ribavirin is contraindicated.
- telaprevir in combination with peginterferon alfa and ribavirin for people with genotype 1 chronic hepatitis C.
- boceprevir in combination with peginterferon alfa and ribavirin for people with genotype 1 chronic hepatitis C.
- sofosbuvir in combination with ribavirin, with or without peginterferon alfa, as an option for specific people with genotypes 1–6 chronic hepatitis C.
- simeprevir in combination with peginterferon alfa and ribavirin as an option for people with genotype 1 or 4 chronic hepatitis C
- ledipasvir–sofosbuvir as an option for specific people with genotype 1 or 4 chronic hepatitis C
- daclatasvir in combination with sofosbuvir, with or without ribavirin, as an option for specific people with genotype 1, 3 or 4 chronic hepatitis C
- daclatasvir in combination with peginterferon alfa and ribavirin, as an option for specific people with genotype 4 chronic hepatitis C
- ombitasvir–paritaprevir–ritonavir with or without dasabuvir or ribavirin as an option for genotype 1 or 4 chronic hepatitis C.

The technology

Sofosbuvir-velpatasvir (brand name unknown, Gilead Sciences) is an oral, fixed-dose combination of 2 anti-hepatitis C virus drugs. Sofosbuvir is a pan-genotypic nucleotide analogue that inhibits the non-structural protein 5B (ns5b), and velpatasvir is a pan-genotypic NS5A inhibitor.

Sofosbuvir-velpatasvir does not currently have a marketing authorisation in the UK for treating chronic hepatitis C. It has been studied in clinical trials, with or without ribavirin, for treating genotypes 1–6 HCV in adults with or

without cirrhosis. The clinical trials included people with untreated HCV and those with previously treated HCV.

Intervention(s)	Sofosbuvir-velpatasvir
Population(s)	Adults with chronic hepatitis C: • who have not had treatment for chronic hepatitis C before (treatment-naive) • who have had treatment for chronic hepatitis C before (treatment-experienced)
Comparators	• best supportive care (watchful waiting) (genotypes 1-6) • boceprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only) • daclatasvir in combination with peginterferon alfa and ribavirin (for specific people with genotype 4; as recommended by NICE) • daclatasvir in combination with sofosbuvir, with or without ribavirin (for specific people with genotype 1, 3 or 4; as recommended by NICE) • ledipasvir–sofosbuvir (for specific people with genotype 1 or 4; as recommended by NICE) • ombitasvir–paritaprevir–ritonavir with or without dasabuvir or ribavirin (for genotype 1 or 4) • peginterferon alfa with ribavirin (for genotypes 1-6) • simeprevir in combination with peginterferon alfa and ribavirin (for genotype 1 or 4) • sofosbuvir in combination with ribavirin, with or without peginterferon alfa (for specific people with genotypes 1-6; as recommended by NICE) • telaprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only)

Outcomes	The outcome measures to be considered include: • sustained virological response • development of resistance to treatment • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows the following subgroups will be considered: • genotype • co-infection with HIV • people with and without cirrhosis • 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 interferon treatment. If the evidence allows, the impact of treatment on reduced onward HCV transmission will also be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related Technology Appraisals**: Ombitasvir/paritaprevir/ritonavir with or without

and NICE Pathways	dasabuvir for treating chronic hepatitis C (2015) NICE Technology appraisal 365. Review date to be confirmed. Daclatasvir for treating chronic hepatitis C (2015) NICE Technology appraisal 364. Review date to be confirmed. Ledipasvir-sofosbuvir for treating chronic hepatitis C (2015) NICE Technology appraisal 363. Review date to be confirmed. Simeprevir in combination with sofosbuvir for treating chronic hepatitis C (2015) Terminated NICE Technology appraisal 361. Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C (2015) NICE Technology appraisal 331. Review date to be confirmed. Sofosbuvir for treating chronic hepatitis C (2015) NICE Technology appraisal 330. Review date to be confirmed. Boceprevir for the treatment of genotype 1 chronic hepatitis C (2012) NICE Technology appraisal 253. Review date to be confirmed. Telaprevir for the treatment of genotype 1 chronic hepatitis C (2012) NICE Technology appraisal 252. Review date to be confirmed. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (2010) NICE Technology appraisal 200. Added to static list December 2013. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C' (partially updated in TA200) (2006) NICE Technology appraisal 106. Added to static list December 2013. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C' (partially updated in TA200) (2004) NICE Technology appraisal 75. Added to static list December 2013. **Related guidelines**: *Guideline in development* Hepatitis C: Diagnosis and management of hepatitis C Publication date to be confirmed **Related Public Health Guidance**: Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (2012) NICE Public Health Guidance 43 Needle and syringe programmes (2009) NICE Public

	Health Guidance 18 **Related Quality Standards**: Quality standard for drug use disorders (2012) NICE quality standard 23 http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp **Related NICE Pathways**: Hepatitis B and C testing (2012) NICE pathway http://pathways.nice.org.uk/pathways/hepatitis-b-and-c-testing Liver conditions NICE pathway http://pathways.nice.org.uk/pathways/liver-conditions
Related National Policy	NHS England, Manual for prescribed specialised services for 2013/14, Chapter 65, Jan 2014. http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf NHS England, Clinical Commissioning Policy Statement: Treatment of chronic Hepatitis C in patients with cirrhosis. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/06/hep-c-cirrhosis-polcy-statmnt-0615.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

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Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Gilead Sciences (sofosbuvir-velpatasvir) Patient/carer groups • Addaction • Addiction Today (Addiction Recovery Foundation) • ADFAM • African Health Policy Network • Black Health Agency • British Liver Trust • Compass UK • GMFA - The Gay Men's Health Charity • Haemophilia Alliance • Haemophilia Society • Hepatitis C Trust • HIV i Base • Lifeline Project • Liver4Life • Muslim Council of Britain • NAM Publications • National AIDS Trust • Positively UK • South Asian Health Foundation • Specialised Healthcare Alliance • Terrence Higgins Trust • UK Harm Reduction Alliance • UK Thalassaemia Society Professional groups • Association for Clinical Biochemistry and Laboratory Medicine • British Association for Sexual Health	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Drugs Action (Scotland) • Healthcare Improvement Scotland • Hospital Information Services – Jehovah's Witnesses • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Blood and Transplant • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Scottish Viral Hepatology Group Comparator companies • Abbvie (ombitasvir, paritaprevir, ritonavir, and dasabuvir) • Bristol-Myers Squibb (daclatasvir) • Gilead Sciences (sofosbuvir, ledipasvir/sofosbuvir • Janssen (simeprevir, telaprevir) • Meda Pharmaceuticals (ribavirin) • Merck Sharp & Dohme (boceprevir, peginterferon alfa 2b, ribavirin) • Mylan UK (ribavirin) • Roche Products (peginterferon alfa 2a,

Consultees	**Commentators (no right to submit or appeal)**
and HIV • British Association for the Study of the Liver (BASL) • British Association for the Study of the Liver Nurses Forum • British Geriatrics Society • British HIV Association • British Infection Association • British Society of Gastroenterology • British Transplantation Society • British Viral Hepatitis Group • HCV Action • Haemophilia Nurses Association • Hepatitis Nurse Specialist Forum • Infection Prevention Society • Medical Foundation for AIDS & Sexual Health • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Society for General Microbiology • UK Clinical Pharmacy Association • UK Clinical Virology Network • UK Haemophilia Centre Doctors' Association <u>Others</u> • Department of Health • NHS England • NHS Southend CCG • NHS Tameside and Glossop CCG • Welsh Government	ribavirin) Teva UK (ribavirin) <u>Relevant research groups</u> • Cochrane Hepato-Biliary Group • Foundation for Liver Research • HCV Research UK • MRC Clinical Trials Unit • National Institute of Health Research • STOP-HCV UK • UCL Centre for Sexual Health & HIV Research • UK National Screening Committee <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations

from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: of the companies that markets comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID 921]

Company evidence submission

September 2016

File name	Version	Contains confidential information	Date
ID921_Gilead_sofosbuvir velpatasvir_submission of evidence	7.0	Yes	7th September 2016

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 250 pages, excluding appendices and the pages covered by this template.

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.

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Abbreviations

AE	Adverse event
ART	Anti-retroviral therapy
BOC	Boceprevir
CEAC	Cost-effectiveness acceptability curve
CHC	Chronic hepatitis C
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
CIC	Commercial-in-confidence
CMH	Cochran-Mantel-Haenszel
CPT	Child-Pugh-Turcotte
CrI	Credible interval
CSR	Clinical study report
CYP	Cytochrome P450
DAA	Direct acting antiviral
DCC	Decompensated cirrhosis
DCV	Daclatasvir
DSV	Dasabuvir
DSA	Deterministic sensitivity analysis
DNA	Deoxyribonucleic acid
eGFR	Estimated glomerular filtration rate
EASL	European Association for the Study of the Liver
EOT	End of treatment
FAS	Full analysis set
FDC	Fixed dose combination
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
ITC	Indirect treatment comparison
MELD	Model for End-Stage Liver Disease

NHS	National Health Service
NS5A	Non-structural protein 5A
NS5B	Non-structural protein 5B
OBV	Ombitasvir
OD	Once daily
Peg-IFN	Pegylated interferon
PI	Protease inhibitor
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PTV	Paritaprevir
QALY	Quality adjusted life year
RBV	Ribavirin
RNA	Ribonucleic acid
RCT	Randomised controlled trial
RTV	Ritonavir
SAS	Safety analysis set
SmPC	Summary of product characteristics
SMV	Simeprevir
SOF	Sofosbuvir
STR	Single tablet regimen
SVR	Sustained virologic response
TA	Technology appraisal
TE	Treatment-experienced
TN	Treatment-naïve
TP	Transition probability
TVR	Telaprevir
VEL	Velpatasvir

1 Executive summary

Burden of disease and unmet need

Hepatitis C is a progressive infectious life-threatening disease caused by hepatitis C virus (HCV) infecting the liver. Six major HCV genotypes (GT) are prevalent (GT1–6) (1, 2), with GT1 (47%) and GT3 (44%) predominating in England (3). Left untreated, patients with chronic disease are at progressive risk of liver fibrosis, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC) and death (1), as well as extrahepatic diseases including circulatory diseases, renal diseases, autoimmune disorders, cutaneous manifestations and non-liver cancers (4, 5). The rate at which liver disease progresses is unpredictable and related to a range of factors, including alcohol consumption, age at infection, gender, the presence of co-morbidities, and co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) (1). Some genotypes are more difficult to treat than others; of particular significance is that patients infected with GT3 HCV are at increased risk of disease progression compared with other genotypes, with several studies showing significantly higher rates of fibrosis progression (p=0.007) (6), development of HCC (p=0.003) (7) and all-cause mortality (p=0.01) (8). These findings highlight the critical importance of diagnosing and curing chronic hepatitis C (CHC) patients when they are at early stages of disease, to avoid long-term clinical complications.

Historically patients with CHC were poorly served, with NICE-recommended regimens limited to pegylated interferon (Peg-IFN) + ribavirin (RBV) alone, or the first-generation protease inhibitors (PIs), boceprevir (BOC) and telaprevir (TVR), both taken in combination with Peg-IFN+RBV (9-13). However, Peg-IFN and RBV are limited by low sustained virologic response (SVR) rates (40–50% with Peg-IFN+RBV in GT1 (14)), significant side effects (14, 15), contraindications in a number of patient groups (15-17) including those on anti-retroviral therapy (ART) (16, 17), the need for safety and efficacy monitoring and support (14, 18), high discontinuation rates due to adverse events (AEs) (19), long duration of treatment (up to 48 weeks for Peg-IFN+RBV) (16, 17), and administration burden (weekly subcutaneous injections [Peg-IFN] (16, 17) or multiple tablets daily [RBV] (15)). As such, CHC therapy has proved difficult for many patients and limits the proportion that start or complete therapy (18); in a UK setting [redacted] (20).

With the emergence of direct acting antiviral (DAA) -based regimens there has been a move towards regimens that are generally easier to take and are more tolerable. Some of the current NICE-recommended DAA-based regimens provide simpler, short duration, RBV-free options, with up to 100% SVR rates for non-cirrhotic GT1 patients (21-24). However, there is still a reliance on RBV, and in some cases Peg-IFN, or longer treatment durations to achieve high (≥90%) SVR rates in GT2–6 patients, GT1 cirrhotic patients, and other difficult to treat subgroups, such as those with decompensated cirrhosis (21-24). In addition, many DAAs, including simeprevir (SMV), daclatasvir (DCV) and ombitasvir (OBV)/ paritaprevir (PTV)/ ritonavir (RTV), and dasabuvir (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 (22, 23, 25, 26).

Therefore, despite recent advances, there still remains substantial unmet need for simple, short duration, RBV- and Peg-IFN-free, highly effective, pan-genotypic and well tolerated therapies.

Groups that are still of particular concern are those for whom high SVR rates are more difficult to achieve and thus are considered more difficult to treat. These patients groups include:

- GT3 infection
- compensated and decompensated cirrhosis
- ineligible for Peg-IFN
- ineligible for RBV
- CHC treatment-experienced

Unmet need in GT3

Chronic GT3 infection arguably represents the area of greatest unmet clinical need, because of the size and additional morbidity associated with this particular genotype. GT3 accounts for around 44% of all HCV infections in England (3). Furthermore, several studies have shown that patients with GT3 HCV infection experience significantly higher rates of fibrosis progression (p=0.007) (6), development of HCC (p=0.003) (7) and all-cause mortality (p=0.01) (8), compared with patients infected with other HCV genotypes.

In spite of this, and the recent advances in treatment regimens for other genotypes, there are still very limited NICE-recommended DAA-based options available for GT3 overall. In GT3 patients who are treatment-naïve and without cirrhosis the situation is even more urgent, with no interferon (IFN)-free or RBV-free treatment available that is recommended by NICE for all patients, leaving only Peg-IFN+RBV or no treatment as the viable options. Treatment outcomes for GT3 patients treated with Peg-IFN+RBV are poor, with real-world data in England showing [redacted](20).

Sofosbuvir/Velpatasvir

Aside from having the potential to fulfil this significant unmet clinical need in GT3 treatment-naïve, non-cirrhotic patients, the availability of a pan-genotypic, short duration, IFN- and RBV-free treatment option such as sofosbuvir (SOF)/ velpatasvir (VEL) creates a realistic opportunity to eliminate the burden of HCV infection in England and Wales. This value of SOF/VEL to the healthcare system in England and Wales is even more pronounced in the context of CHC treatment in resource-constrained settings where rapid genotyping of CHC patients may not be practical or feasible. In this context, where SOF/VEL requires no genotyping, it would potentially simplify treatment choice, enabling CHC treatment to be delivered in a greater number and variety of healthcare settings, thereby enabling a greater number of CHC patients to be treated in England and Wales as compared to historic treatment rates.

1.1 *Statement of the decision problem*

The objective of this technology appraisal is to appraise the clinical and cost effectiveness of the combination of SOF/VEL within its marketing authorisation – anticipated date July 2016 – for treating CHC. The NICE decision problem is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale
Population	Adults with CHC • Who have not had treatment for CHC before (treatment-naive) • Who have had treatment for CHC	As per final scope

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale
	before (treatment-experienced)	
Intervention	SOF/VEL	As per anticipated marketing authorisation • SOF/VEL 12 weeks for all patients without cirrhosis or compensated cirrhosis, including those with HIV co-infection. • SOF/VEL+RBV 12 weeks for patients with decompensated cirrhosis
Comparator(s)	• Best supportive care (watchful waiting) (GT1-6) • BOC+Peg-IFN+RBV (for GT1 only) • DCV+Peg-IFN+RBV (for specific people with GT4; as recommended by NICE) • DCV+SOF±RBV (for specific people with GT1, 3 or 4; as recommended by NICE) • LDV/SOF (for specific people with GT1 or 4; as recommended by NICE) • OBV/PTV/RTV±DSV±RBV (for GT1 or 4) • Peg-IFN+RBV (for GT1-6) • SMV+Peg-IFN+RBV (for GT1 or 4) • SOF+RBV±Peg-IFN (for specific people with GT1-6; as recommended by NICE) • TVR+Peg-IFN+RBV (for GT1 only)	As per final scope, with the following exceptions: • All active treatments are included in line with NICE recommendations from technology appraisals • "Best supportive care" is defined as no treatment in this submission ○ "No treatment" modelled in line with previous submissions and in the context of Public Health England data that shows very poor linkage to the care of patients who are diagnosed but not treated (i.e. how "watchful waiting" in the UK context doesn't work with this patient population) • BOC and TVR included by extrapolating from findings for SOF/VEL versus SMV+Peg-IFN+RBV ○ As discussed at the NICE decision problem meeting, BOC and TVR are rarely used in the NHS, having been superseded by SMV. Neither BOC nor TVR have been included in Gilead's economic modelling and the modelling approach taken was to extrapolate from the findings of SOF/VEL versus SMV+Peg-IFN+RBV, an approach which NICE agreed was reasonable
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 is discussed only in Section 4 as this outcome does not impact the cost-effectiveness of SOF/VEL, i.e. it has not impact on cost or QALYs
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or	As per final scope. The time horizon for the modelling is a lifetime.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale
	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: • Genotype • Co-infection with HIV • People with and without cirrhosis • 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	Evidence allowed subgroup analyses including: • Genotype • People with and without cirrhosis • People with decompensated cirrhosis
Special considerations including issues related to equity or equality		CHC GT3 patients are characterised by a disproportionately higher number of patients from migrant backgrounds, which could potentially raise an equality issue if these people encounter greater difficulty in achieving access to SOF/VEL

BOC, boceprevir; CHC, chronic hepatitis C; DCV, daclatasvir; DSV, dasabuvir; GT, genotype; HRQL, health-related quality of life; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; Peg-IFN, pegylated interferon; PTV, paritaprevir; QALY, quality adjusted life year; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TVR, telaprevir; VEL, velpatasvir

1.2 *Description of the technology being appraised*

SOF/VEL fixed dose combination (FDC) is the first pan-genotypic single tablet regimen (STR) for the treatment of CHC, providing a simple, all-oral, once-daily, Peg-IFN- and RBV-free treatment option for all adult patients, including those with compensated cirrhosis. In addition, by adding RBV to the regimen, patients with decompensated cirrhosis can also be treated.

SOF/VEL combines SOF, a pan-genotypic inhibitor of the HCV non-structural protein 5B (NS5B) ribonucleic acid (RNA)-dependent RNA polymerase, which is essential for viral replication, and VEL, a HCV inhibitor targeting the HCV non-structural protein 5A (NS5A) protein, which is essential for both RNA replication and the assembly of HCV virions.

Table 2: Technology being appraised

UK approved name and brand name	Sofosbuvir velpatasvir (SOF/VEL) 400 mg/100 mg film-coated tablets Brand name: To be confirmed
Marketing authorisation/CE mark status	Marketing authorisation anticipated July 2016

Indications and any restriction(s) as described in the summary of product characteristics	SOF/VEL is indicated for the treatment of chronic HCV infection in adults. The licensed indication for SOF/VEL covers chronic HCV infection of any genotype (GT1–6) in patients without cirrhosis, those with compensated cirrhosis and those with decompensated cirrhosis. Eligible patients may also include those with HCV/HIV co-infection. Contraindications are limited to hypersensitivity to the active substances or excipients listed in the SmPC. Patients taking concomitant amiodarone should be closely monitored. The safety of SOF/VEL has not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or end-stage renal disease requiring haemodialysis. There are no data on the use of SOF/VEL in patients with HCV/HBV co-infection or in patients who are post-liver transplant. The concomitant use of potent inducers of P-glycoprotein and/or moderate to potent inducers of CYP2B6, CYP2C8 or CYP3A4 is not recommended. SOF/VEL is not recommended for use in children and adolescents.
Method of administration and dosage	Each film-coated tablet contains 400 mg SOF and 100 mg VEL. SOF/VEL is taken orally as a single tablet, once daily. ***Patients without cirrhosis and patients with compensated cirrhosis:*** • SOF/VEL for 12 weeks ***Patients with decompensated cirrhosis:*** • SOF/VEL+RBV for 12 weeks

GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SOF, sofosbuvir; VEL, velpatasvir

1.3 *Summary of the clinical effectiveness analysis*

SOF/VEL has been studied in a comprehensive clinical trial programme consisting of:

- Three pivotal randomised, placebo- or active-controlled Phase III studies covering adult patients with CHC who were CHC treatment-naïve or treatment-experienced, and included those with compensated cirrhosis (ASTRAL-1, -2 and -3),
- One Phase III randomised study in decompensated patients (ASTRAL-4) and
- One ongoing Phase III randomised study in patients co-infected with HCV/HIV (ASTRAL-5)

Of the three pivotal Phase III studies:

- ASTRAL-3 provides comparative evidence versus SOF+RBV 24 weeks for the use of SOF/VEL for 12 weeks in patients with HCV GT3 infection, a key population with high unmet need and the focal population of this submission.
- ASTRAL-2 provides comparative evidence versus SOF+RBV 12 weeks for the use of SOF/VEL for 12 weeks in patients with HCV GT2 infection, using identical methodology to that employed for ASTRAL-3.
- ASTRAL-1 provides comparative evidence versus placebo for the use of SOF/VEL for 12 weeks in patients with HCV GT1, GT2, GT4, GT5, or GT6 infection, with similar methodology to that employed in ASTRAL-2 and -3.

Pan-genotypic efficacy

ASTRAL-1, -2 and -3 show that very high cure rates (SVR12) of 89–100% can be achieved in adult patients with CHC GT1–6 infection with SOF/VEL administered as an STR once daily for

12 weeks (Section 4.7). In ASTRAL-2 and ASTRAL-3, SVR12 rates were significantly superior to the active comparator SOF+RBV (12 weeks, ASTRAL-2; 24 weeks, ASTRAL-3). In ASTRAL-1 SVR12 was significantly superior to the pre-defined performance goal of 85%.

High cure rates were achieved irrespective of cirrhotic status (without cirrhosis or with compensated cirrhosis) or prior CHC treatment experience (treatment-naïve or treatment-experienced) (Section 4.8). These are characteristics which historically have been linked with poor response to IFN-containing regimens (27), and which, in the current era of DAAs still limit the effectiveness of some treatment regimens, including SOF+RBV (28).

Furthermore, some patients 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 3.3), SOF/VEL provides an IFN-free and RBV-free treatment option that is highly effective across all genotypes.

GT3 infection

In particular, SOF/VEL is a treatment option that can fulfil the substantial unmet clinical need identified in GT3 patients. In ASTRAL-3 SOF/VEL provided SVR rates that were consistently higher than the active comparator of SOF+RBV for 24 weeks ranging from 98% in treatment-naïve without cirrhosis; 93% in treatment-naïve with cirrhosis: 91% in treatment-experienced without cirrhosis and 89% in treatment-experienced with cirrhosis (see Section 4.8).

The only NICE-recommended treatment regimen available for all GT3 patients is Peg-IFN+RBV for 24 weeks, but SVR rates are poor (e.g. 63% in treatment-naïve patients including those with compensated cirrhosis (19)) and treatment with Peg-IFN+RBV is associated with significant limitations from a tolerability and monitoring perspective, that limit its utility in clinical practice (14, 18, 20). Current NICE-recommended DAAs have varying efficacy in GT3 infection, and NICE have limited their use to specific subgroups, based on prior treatment experience, cirrhotic status and IFN eligibility (see Section 3.3). In this context, the finding that SVR rates are consistently high with SOF/VEL across patient subgroups, including those with cirrhosis and prior treatment failure, represents an improvement in outcome over current treatment options, along with a shorter duration of treatment in some cases and fewer side effects owing to the removal of Peg-IFN and/or RBV from the regimen. As such, SOF/VEL provides a real opportunity to specifically address the substantial unmet need in this patient group.

Decompensated cirrhosis

For adult patients with more advanced liver disease (decompensated cirrhosis), the addition of RBV to the SOF/VEL treatment regimen (12 weeks treatment) also enables high cure rates (SVR12 94%) to be achieved (ASTRAL-4) (Section 4.11).

Other efficacy endpoints

Across the ASTRAL randomised controlled trials (RCTs) (ASTRAL-1, -2, -3) treatment with SOF/VEL resulted in a rapid and sustained decline in HCV RNA levels, with >90% of patients achieving a virologic response below the level of quantification after 4 weeks of treatment. This response negates the need for on-treatment monitoring of HCV RNA or response-guided therapy for SOF/VEL regimens and is in contrast to other therapies, such as Peg-IFN and PI-based regimens.

Of 1,035 patients randomised to and receiving at least one dose of SOF/VEL in ASTRAL-1, -2 and -3 (full analysis set [FAS]), 98.1% (1,015) were cured of their CHC, 1.3% (13) experienced virologic relapse after treatment, none experienced on-treatment failure and 0.7% (7) were lost to follow-up, discontinued due to AEs or died.

SOF/VEL has a high barrier to the development of treatment-resistant mutations. Deep sequencing showed that, of the 13 patients experiencing relapse, none had resistance to SOF. Twelve had NS5A mutations at relapse that could confer resistance to VEL, of which seven had NS5A mutations at study baselines. However, high SVR12 rates were achieved in the presence of baseline NS5A resistance-associated variants, observed in between 16% (ASTRAL-3) and 60% (ASTRAL-2) of the overall study populations. Thus, the presence of resistance associated variants at baseline appears to have poor predictive value for virologic failure when patients are treated with SOF/VEL.

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

Safety and tolerability

The safety and tolerability data from ASTRAL-1, -2 and -3 demonstrate that SOF/VEL is well tolerated; no adverse drug reactions specific to SOF/VEL were identified, with the type, incidence and severity of AEs being comparable to placebo (Section 4.12). Similarly in patients with decompensated cirrhosis (ASTRAL-4) treated with SOF/VEL+RBV for 12 weeks no adverse drug reactions to SOF/VEL were identified, while the AEs observed were consistent with the expected clinical sequelae of decompensated liver disease, or the known toxicity profile of RBV.

1.4 *Summary of the cost-effectiveness analysis*

A Markov state-transition model was adapted from the model by Dusheiko and Roberts (29), and based on the model accepted by NICE for the appraisal for SOF and for LDV/SOF. Patients entered the model in non-cirrhotic, compensated cirrhosis or decompensated cirrhosis health states. Patients who achieve SVR after treatment are considered to be virologically cured and those not achieving SVR either remain in their current health state or progress to more advanced stages of the disease, including decompensated cirrhosis, HCC, liver transplant or death.

The model was used to assess the cost-effectiveness of SOF/VEL (or SOF/VEL+RBV for decompensated cirrhosis) within its licensed indication compared with the treatments listed in Table 1, from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) in England and Wales.

Estimates of relative efficacy to populate the model were sourced in part from the ASTRAL studies – ASTRAL-3 in CHC GT3 provides data for SOF/VEL versus SOF+RBV for 24 weeks and ASTRAL-2 in CHC GT2 provides data versus SOF+RBV for 12 weeks. However, given the large number of treatment regimens available for CHC it is impractical to design trials that compare with all potential comparators, nor to design pan-genotypic trials versus a single standard of care.

At the time of the design of the ASTRAL programme it would not have been clear that there was a definitive standard of care regimen for each disease progression state with which to compare. Where a standard of care was possible to define (in GT2 and GT3), the ASTRAL trials were designed to reflect this. Comparing against more than one other comparator in a Phase III trial, using either a non-inferiority or superiority design is: methodologically difficult; would require very large patient numbers to adequately power; would likely require a follow-up period that was so long that the standard of care would be obsolete by the time the study had enrolled, due to the concurrent development of DAA combinations from multiple manufacturers.

Therefore, the feasibility of undertaking an NMA was explored, as described in Section 4.10. However, only analyses in GT1 treatment-naïve and GT3 treatment-naïve patients were theoretically feasible and these were extremely limited in several key areas. In the GT3 treatment-naïve population specifically, the NMA analysis was compromised by the necessity of including a very small Phase II trial in order to construct the network. In this trial (ELECTRON (30)), all relevant treatment arms (n=13) achieved 100% SVR rates. The efficacy of one of the trial arms (100% SVR for SOF+RBV 12 weeks; n=6) is an outlier which lacks clinical face validity, in that the observed efficacy is at odds with data from large Phase III trials and real world settings; in these trials the SVR rate on SOF+RBV 12 weeks in GT3 patients was 56% in treatment-naïve patients (FISSION (19)) and 30% in treatment-experienced patients (FUSION (31)). Inclusion of the data from ELECTRON therefore contributes to spurious indirect treatment effect estimates across the GT3 treatment-naïve network, with overall results that lack clinical validity. In addition, the proportions of cirrhotic patients in the studies which connected SOF/VEL to the reference treatment in the GT3 treatment-naïve network (Peg-IFN+RBV), varied between 16 and 38% (ASTRAL-3, BOSON, Chulanov AASLD 2014, FISSION), with one study (ELECTRON) having no patients with cirrhosis. Given that METAVIR score is known to be a treatment effect modifier in hepatitis C (14), this variability introduced heterogeneity into the network. Ideally, this heterogeneity would be adjusted for through meta-regression or subgroup analysis. However, meta-regression was not feasible due to inconsistency in reporting of METAVIR score across studies. Specifically, studies which evaluated a mixed population in terms of genotype typically reported baseline characteristics for the whole population, or GT2 and GT3 combined. Subgroup analyses were also not feasible due to the number of disconnections in the network. As such, the impact of heterogeneity in METAVIR score across studies on the estimated relative treatment effects (in terms of SVR) is unknown and hence the strong likelihood is that this would introduce bias. This has been extensively discussed in the submission (see Section 4.10.9) and has been the subject of external clinical expert validation (see Section 5.3.3 clinical validation). Meaningful analyses in other populations were limited by data availability (see Section 4.10.9). Overall, disappointingly the NMA could not provide the necessary relative treatment effects stratified according to patient treatment history and cirrhosis status (as required by the final NICE scope) and the results were not robust enough for use in the economic model. For this reason, as with previous CHC NICE submissions, the economic model was populated with efficacy data from individual studies in all patient groups. This approach was more appropriate, transparent and aligned with the final NICE scope, given that it allowed the economic model to be populated with efficacy data that was stratified by treatment history and cirrhosis status where the available data allowed (see Section 4.10.9 for descriptions of the studies informing the model; Section 5.6.1 for efficacy and safety data derived from these studies).

Summary of economic results

- **The company evidence submission for SOF/VEL made to NICE on the deadline on Friday 20th May 2016 used the proposed confidential fixed price of SOF/VEL, and anticipated list prices of comparators, for all analyses. This approach was aligned with discussion at the Decision Problem meeting for this appraisal on 24th March 2016. Following request from NICE on Thursday 26th May, revised analyses have been prepared, in which:**
  - **the proposed confidential fixed price of SOF/VEL is used for all analyses that do not contain either ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) or daclatasvir**
  - **the anticipated UK anticipated list price of SOF/VEL is used for all analyses containing either ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) or daclatasvir**
- **It was acknowledged by NICE on Thursday 26th May that "the anticipated list price versus anticipated list price analyses would also be non-informative to some extent". Gilead agrees that the analyses using the anticipated UK anticipated list price of Eplcusa will not be informative and that analyses which use the proposed confidential fixed price of SOF/VEL should be the primary analyses considered for appraisal and decision making purposes.**
- **It is also clear that for some of the analyses in which the anticipated UK anticipated list price of SOF/VEL is used, differences in total costs and/or QALYs versus some comparators are extremely small. This renders the corresponding incremental cost-effectiveness ratios extremely sensitive to very small changes in costs and QALYs, which further undermines the usefulness of these results for appraisal and decision making purposes.**
- **Nevertheless, following the request from NICE for these revised analyses (which is considered to be outside of the usual STA process) these have been provided. The title of each results table indicates whether the proposed confidential fixed price of SOF/VEL or the anticipated UK anticipated list price of SOF/VEL has been used in the analysis.**

GT3 (anticipated list price of SOF/VEL IFN ineligible patients only)

- ***For GT3 treatment naïve patients without cirrhosis*** SOF/VEL is highly cost-effective with an incremental cost-effectiveness ratio (ICER) of £15,199 versus Peg-IFN+RBV 24 weeks, with "no treatment" being dominated by Peg-IFN+RBV. In this patient group SOF/VEL provides the first DAA-based regimen that can be used for all patients with GT3 infection who are treatment-naïve without cirrhosis. SOF/VEL provides a highly effective and cost-effective treatment for a group for whom there is substantial unmet clinical need.
- ***For GT3 treatment naïve patients without cirrhosis who are IFN-ineligible***, SOF+DCV 12 weeks is the only DAA-based NICE-recommended regimen available, to which access is further restricted to patients who are F3/F4. In this group SOF/VEL 12 weeks dominates SOF+DCV and has an ICER of £5,287 versus no treatment.
- For all other ***GT3 populations***, including ***treatment-naïve cirrhotic, treatment-experienced non-cirrhotic and treatment-experienced cirrhotic***, SOF/VEL 12 weeks is cost-effective versus no treatment and Peg-IFN+RBV 24/48 weeks with ICERs <£5,000.

SOF+Peg-IFN+RBV 12 weeks is either dominated by SOF/VEL or has an ICER >£100,000.

- For all other ***GT3 IFN-ineligible populations***, including ***treatment-naïve cirrhotic, treatment-experienced non-cirrhotic and treatment-experienced cirrhotic***, SOF/VEL 12 weeks is cost-effective versus no treatment and all active comparators with ICERs <£10,000.

GT1 (anticipated list price of SOF/VEL)

- In ***GT1 treatment-naïve non-cirrhotic*** patients the ICER for SOF/VEL 12 weeks versus no treatment was £7,028 per QALY. The ICER for SOF/VEL compared to LDV/SOF 8 weeks was £73,604
- For all other ***GT1 populations***, including ***treatment-naïve cirrhotic, treatment-experienced non-cirrhotic and treatment-experienced cirrhotic,*** SOF/VEL 12 weeks is cost-effective versus no treatment with ICERs <£10,000. All other regimens are either dominated or dominated by the principle of extended dominance, with the exception of SOF+DCV 12w where the ICER vs SOF/VEL is £398,971.
- For ***sub-genotype analyses in 1a,*** the Abbvie regimens (OBV/PTV/RTV+DSV±RBV 12/24 weeks) were always dominated by SOF/VEL 12 weeks, except in GT1a treatment-experienced non-cirrhotic patients where SOF/VEL has an ICER of £41,741 vs OBV/PTV/RTV+DSV+RBV 12 weeks
- For ***sub-genotype analyses in 1b,*** the Abbvie regimens (OBV/PTV/RTV+DSV±RBV 12 weeks) dominated SOF/VEL.

GT2 (discounted price of SOF/VEL)

- In ***GT2 treatment-naïve non-cirrhotic*** patients SOF/VEL has an ICER of £32,595 versus Peg-IFN+RBV 24 weeks. This ICER is discussed further in Section 5.7.1.1.
- In ***GT2 treatment-naïve cirrhotic*** patients SOF/VEL has an ICER of ~£12,000 versus Peg-IFN+RBV 24 weeks, with no treatment being dominated.
- For ***GT2 treatment-experienced non-cirrhotic and treatment-experienced cirrhotic,*** patients SOF/VEL 12 weeks is cost-effective versus no treatment and Peg-IFN+RBV 48 weeks with ICERs <£7,000. SOF+RBV 12 weeks is either dominated (non-cirrhotic) or has an ICER >£1.7 million (cirrhotic) versus SOF/VEL 12 weeks.
- In analyses of ***GT2 IFN-ineligible*** patients, which include SOF+RBV 12 weeks as an option for treatment-naïve patients, this regimen is dominated by SOF/VEL in both non-cirrhotic and cirrhotic cohorts.

GT4 (anticipated list price of SOF/VEL price for non-cirrhotic patients only)

- In **GT4 non-cirrhotic treatment-naïve and -experienced** patients, the ICER for SOF/VEL was £380,526 per QALY vs ombitasvir/paritaprevir/ritonavir + RBV. In **GT4 cirrhotic treatment-naïve and –experienced** patients SOF/VEL is highly cost-effective with it either dominating other options or having ICERs <£7,000

GT 5/6 (discounted price of SOF/VEL)

- Across all analyses of GT5 and GT6 patients stratified by treatment experience and cirrhotic status, SOF/VEL is highly cost-effective with it either dominating other options or having ICERs <£7,000.

Decompensated cirrhosis (discounted price of SOF/VEL)

- For decompensated patients, the current treatment option available is LDV/SOF+RBV for 12 weeks. In both treatment-naïve and treatment-experienced patients SOF/VEL+RBV 12 weeks is both cheaper and more efficacious, meaning that it dominates this current standard of care.

Sensitivity analysis

Comprehensive sensitivity analyses, in the form of probabilistic sensitivity analysis (PSA), deterministic sensitivity analysis (DSA) and scenario analyses were conducted to explore the impact of parameters and any structural uncertainty within the model. The model was found to be robust, and probabilistic results were consistent with the base case analysis. When including additional comparators within scenario analyses, these had no bearing on the estimates of cost-effectiveness of SOF/VEL, and were almost always dominated.

Conclusion

SOF/VEL, the first pan-genotypic STR for the treatment of CHC, provides a simple, all-oral, once-daily, short duration, Peg-IFN- and RBV-free treatment option for all adult patients, including those with compensated cirrhosis. In addition, SOF/VEL specifically addresses the substantial unmet clinical need in patients with GT3 CHC who are treatment-naïve without cirrhosis. By adding RBV to the regimen, patients with decompensated cirrhosis can also be treated.

The availability of SOF/VEL creates a realistic opportunity to eliminate the burden of HCV infection in England and Wales. This value of SOF/VEL to the healthcare system in England and Wales is even more pronounced in the context of CHC treatment in resource-constrained settings where rapid genotyping of CHC patients may not be practical or feasible. In this context, where SOF/VEL requires no genotyping, it would potentially simplify treatment choice, enabling CHC treatment to be delivered in a greater number and variety of healthcare settings, thereby enabling a greater number of CHC patients to be treated in England and Wales as compared to historic treatment rates.

2 The technology

2.1 *Description of the technology*

Brand name: Epclusa

UK approved name: Sofosbuvir velpatasvir (SOF/VEL) 400 mg/100 mg film-coated tablets.

Therapeutic class: DAA: HCV NS5A inhibitor (VEL); uridine nucleotide analogue NS5B polymerase inhibitor (SOF).

Mechanism of action:

SOF is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential 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 RNA by the NS5B polymerase and acts as a chain terminator. GS-461203 (the active metabolite of SOF) is neither an inhibitor of human deoxyribonucleic acid (DNA) and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

VEL is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. In vitro resistance selection and cross-resistance studies indicate VEL targets NS5A as its mode of action.

2.2 *Marketing authorisation and health technology assessment*

2.2.1 *Marketing authorisation*

[redacted]

2.2.2 *(Anticipated) indication(s) in the UK*

SOF/VEL is indicated for the treatment of chronic HCV infection in adults.

The licensed indication for SOF/VEL covers chronic HCV infection of any genotype (GT1–6) in patients without cirrhosis, those with compensated cirrhosis and those with decompensated cirrhosis. Eligible patients may also include those with HCV/HIV co-infection.

2.2.3 *(Anticipated) restrictions or contraindications*

Contraindications, special warnings and precautions for use are listed as per the draft summary of product characteristics (SmPC) (See Appendix 1).

Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in Section 6.1 of the product SmPC.

Special warnings and precautions for use

SOF/VEL should not be administered concurrently with other medicinal products containing SOF.

Severe bradycardia and heart block

Cases of severe bradycardia and heart block have been observed when SOF, used in combination with another DAA, is used with concomitant amiodarone with or without other drugs that lower heart rate. The mechanism has not been established.

The concomitant use of amiodarone was limited through the clinical development of SOF plus DAAs. Cases are potentially life threatening, therefore amiodarone should only be used in patients on SOF/VEL when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated.

Should concomitant use of amiodarone be considered necessary, it is recommended that patients are closely monitored when initiating SOF/VEL. Patients who are identified as being high risk of bradyarrhythmia should be continuously monitored for 48 hours post treatment initiation in an appropriate clinical setting.

Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on SOF/VEL.

All patients receiving SOF/VEL in combination with amiodarone with or without other drugs that lower heart rate should also be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

Renal impairment

No dose adjustment of SOF/VEL is required for patients with mild or moderate renal impairment. The safety of SOF/VEL has not been established in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) or end-stage renal disease requiring haemodialysis. When SOF/VEL is used in combination with RBV refer also to the SmPC for RBV for patients with creatinine clearance <50 mL/min.

Use with potent inducers of P-glycoprotein and/or moderate to potent inducers of cytochrome P450

Medicinal products that are potent inducers of P-glycoprotein and/or moderate to potent inducers of CYP2B6, CYP2C8 or CYP3A4 (e.g. rifampicin, St. John's wort, carbamazepine and phenytoin) may significantly decrease plasma concentrations of SOF and/or VEL leading to reduced therapeutic effect of SOF/VEL. The use of such medicinal products with SOF/VEL is not recommended.

HCV/HBV co-infection

There are no data on the use of SOF/VEL in patients with HCV/HBV co-infection.

Liver transplant patients

The safety and efficacy of SOF/VEL in the treatment of HCV infection in patients who are post-liver transplant have not been established.

Paediatric population

SOF/VEL is not recommended for use in children and adolescents under 18 years of age because the safety and efficacy have not been established in this population.

2.2.4 *SmPC/Information for use and (Draft) assessment report*

Draft SmPC and (Draft) EPAR are provided in Appendix 1.

2.2.5 *Main issues discussed by regulatory authorities*

CHMP positive opinion for SOF/VEL was granted on 26th May 2016; however, the draft EPAR and SmPC have not yet been published and a summary of the issue discussed is therefore not available. It is not anticipated that special conditions will be attached to the marketing authorisation.

2.2.6 *Anticipated date of availability in the UK*

The launch date of SOF/VEL is anticipated shortly after marketing authorisation has been granted.

2.2.7 *Regulatory approval outside the UK*

Marketing authorisation has been sought for SOF/VEL from the CHMP, via the centralised process, for the 28 EU states, Iceland, Norway, and Liechtenstein. Milestone dates are provided in Section 2.2.1.

In addition, regulatory approval for SOF/VEL has been sought in the USA (anticipated approval in June 2016); Canada (anticipated approval in July 2016), and in Australia (anticipated approval in January 2017).

2.2.8 *Ongoing HTAs in the rest of the UK*

Submission to the Scottish Medicines Consortium is currently planned for June 6th 2016.

2.3 *Administration and costs of the technology*

Table 3: Costs of the technology being appraised

	Information	Source
Pharmaceutical formulation	Film-coated tablet containing 400 mg SOF and 100 mg VEL	SmPC Section 2
Acquisition cost (excluding VAT)	SOF/VEL 28 tablets: • £12,993.33 (Anticipated list price) [redacted] In patients with decompensated cirrhosis it is recommended that SOF/VEL be given in combination with RBV RBV 56x400 mg tablets: £246.65	BNF, 23rd March 2016
Method of administration	Oral	SmPC Section 4.2
Doses	400 mg SOF and 100 mg VEL as a single tablet	SmPC Section 2, 4.2
Dosing frequency	Once daily	SmPC Section 4.2
Average length of a course of treatment	Patients without cirrhosis and patients with compensated cirrhosis • SOF/VEL for 12 weeks Patients with decompensated cirrhosis • SOF/VEL+RBV for 12 weeks	SmPC Table 1, Section 4.2
Average cost of a course of treatment	SOF/VEL 12 weeks: £38,980 (list); [redacted] SOF/VEL+RBV 12 weeks: £40,089.93 (list); [redacted]	
Anticipated average interval between courses of treatments	Not applicable	
Anticipated number of repeat courses of treatments	Not applicable	
Dose adjustments	Dose adjustments are not recommended	SmPC Section 4.2, 4.5
Anticipated care setting	Patients will be initiated and monitored in secondary care only	

RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

2.3.1 *Patient access scheme*

A commercial-in-confidence price proposal has been made to NICE for SOF/VEL. This proposal fulfils the criteria for consideration as a Simple Discount Agreement and has been submitted to PASLU. The proposal makes SOF/VEL available to the NHS at a CIC price of [redacted] per bottle of 28 tablets, from the date of technology appraisal guidance publication by NICE.

2.4 *Changes in service provision and management*

2.4.1 *Additional test/investigations*

No tests or investigations are required in addition to current routine hepatitis tests.

2.4.2 *Main resource use to the NHS associated with the technology*

SOF/VEL is administered orally, and as such there are no additional costs associated with administration of SOF/VEL, compared with other treatments for CHC. In addition, resource required for monitoring may be reduced compared with some current treatments, resulting from elimination of response-guided therapy and an improved tolerability profile (see Section 2.4.4).

Further details on resource costs will be provided in Section 6.

2.4.3 *Additional infrastructure requirements*

Treatment for patients with CHC is routinely delivered through Operational Delivery Networks that have been put in place by NHS England. Given that treatment duration and AEs may be reduced with SOF/VEL compared with some current treatments (such as those that include Peg-IFN and/or RBV), it is expected that pressures on the current infrastructure may be reduced.

2.4.4 *Patient monitoring requirements*

In patients taking amiodarone

As described in Section 2.2.3, cases of severe bradycardia and heart block have been observed when SOF, used in combination with another DAA, is used with concomitant amiodarone with or without other drugs that lower heart rate. For patients taking amiodarone who have no other viable treatment option and who will be co-administered SOF/VEL, cardiac monitoring for the first 48 hours of co-administration is recommended in an appropriate clinical setting. In addition, due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on SOF/VEL.

These requirements for monitoring in patients receiving amiodarone are consistent with other SOF-based therapies routinely used in current clinical practice (SOF and LDV/SOF (21, 24)).

Response-guided therapy and AE monitoring

Compared with some existing regimens, SOF/VEL may be expected to reduce monitoring requirements:

- There is no requirement for response-guided therapy with SOF/VEL.
    - Patients treated with Peg-IFN or first generation PI-based regimens (TVR, BOC) are managed using a complex response-guided therapy approach, where virologic response measured at specific time points is used to determine the on-treatment response, likelihood of SVR and the required treatment duration (16, 17, 32, 33).
    - In comparison to Peg-IFN or PI-based regimens, a very high proportion of patients treated with SOF/VEL achieve a rapid virologic response (≥99% after 8 weeks of treatment; see Section 4.7). As a result, monitoring associated with early stopping rules is not required. This should simplify patient management considerably relative to these specific current therapies and also reduce the need for frequent on-treatment viral load monitoring and clinic visits.
- Peg-IFN, PIs and RBV all require careful AE monitoring during treatment, including haematological monitoring (15-17, 32, 33), for progression/resolution of rashes (TVR,

SMV (26, 32)), for signs or symptoms of psychiatric disorders, central nervous system effects, hepatic decompensation, development of gout, and dental and periodontal disorders (Peg-IFN+RBV (15)). With SOF/VEL there is no specific requirement for haematological monitoring and only fatigue and headache were identified as more common in patients treated with SOF/VEL compared with placebo. This safety profile for SOF/VEL should reduce monitoring and AE costs versus Peg-IFN-, PI- and RBV-containing therapies while on treatment. Although it is recommended that SOF/VEL is taken in combination with RBV in patients with decompensated cirrhosis, the majority of patients – those without cirrhosis or with compensated cirrhosis – can be effectively treated with SOF/VEL alone, without the addition of RBV.

2.4.5 *Need for concomitant therapies*

RBV is recommended in combination with SOF/VEL in patients with decompensated cirrhosis (See SmPC Table 1).

2.5 *Innovation*

SOF/VEL FDC is the first pan-genotypic STR for the treatment of CHC. This pan-genotypic coverage, coupled with uniformly high SVR rates observed across genotypes (including in the traditionally difficult to treat GT3 population), may enable the technology to be used in circumstances where the availability of genotyping is limited either by logistical convenience or by clinical expertise to interpret and take action based upon the results. In addition, the EMA has adopted an accelerated regulatory process for SOF/VEL FDC, a designation only granted to those medicines of major public health interest. The decision to adopt the accelerated regulatory process for SOF/VEL was primarily based on the CHMP opinion that there was an unmet medical need for GT3 cirrhotic patients, and a RBV-free treatment option for GT2 patients.

SOF/VEL FDC fulfils a number of criteria identified by the Kennedy Report as constituting innovation (34):

- SOF/VEL offers a single-tablet treatment regimen for all patients with CHC without cirrhosis or with compensated cirrhosis, removing the requirement for injectable Peg-IFN or oral RBV treatment (and their associated adverse events) in these patients. Therefore, SOF/VEL has the potential to significantly and substantially improve the care of patients with CHC, especially those patients infected with HCV GT3, the majority of whom do not have access to an all-oral CHC treatment at the present time
- SOF/VEL FDC meets a need which the NHS has identified as being important, as evidenced by the recent NHS Outcomes Framework that reflects the government commitment to reducing mortality due to liver disease in people under 75 years of age (35). By providing a cure for the majority of patients, treatment with SOF/VEL has the potential to reduce HCV related-liver disease and associated mortality
- SOF/VEL has a robust and extensive evidence base, and has demonstrated an appropriate level of effectiveness in clinical trials
    - >94% SVR12 rates, equivalent to a cure, for licensed regimens/treatment durations across all HCV genotypes in patients without cirrhosis, with compensated or decompensated cirrhosis
- SOF/VEL will have a marketing authorisation for the indication under review

As CHC is an infectious disease with the potential for cure, by improving cure rates (i.e. SVR rates) together with increasing numbers of patients eligible for treatment, there is the potential to positively impact on the overall epidemiology and long-term burden of CHC to the NHS. In addition, there are potential health-related benefits from a public health perspective that are unlikely to be captured in the quality adjusted life year (QALY) calculation, including:

- reduction in onward transmission of HCV due to effective treatment
- reversal of liver fibrosis once cured

Reduction of onward transmission:

A very high proportion of patients treated with SOF/VEL achieve a rapid virologic response (≥99% after 8 weeks of treatment; see Section 4.7). Public health information regarding transmission from individuals infected with HCV suggests that rapid reduction of the virus through treatment can reduce onward transmission. Specifically, patients who inject drugs represent the main source of HCV transmission and the risk of transmission remains high even when there is high coverage of prevention interventions, such as needle and syringe programmes and opioid substitution treatment (36, 37). Injecting drug users tend not to be treated for their HCV infection because of the risk of re-infection; however modelling analyses by Martin et al suggest that CHC treatment can have an important role in preventing transmission in these populations and that this approach can be a cost-effective policy (38-40). In their recent UK study, Martin et al estimated that treatment with IFN-free DAAs could result in an absolute reduction in HCV chronic prevalence of at least 15% in people who inject drugs (36). Simpler, single tablet, once daily regimens may make it easier for patients who inject drugs to take and benefit from CHC treatment.

Regression of liver fibrosis and reduction in risk of HCC:

A published evidence review from Ng et al identified several studies showing that an SVR can lead to regression of fibrosis and cirrhosis and that these effects are seen in patients with varying degrees of fibrosis (41). The evidence showed that an SVR reduces liver-related mortality among patients with CHC by 3.3- to 25-fold, reduces the incidence of HCC by 1.7- to 4.2-fold, and reduces the incidence of hepatic decompensation by 2.7- to 17.4-fold (41).

3 Health condition and position of the technology in the treatment pathway

3.1 *Disease overview*

Hepatitis C is a progressive infectious disease caused by HCV infecting the liver; the main route of transmission is through exposure to infected blood (1). There are six major HCV RNA genotypes (GT1–6) and multiple subtypes (labelled a, b, c, etc.) characterised by high RNA sequence heterogeneity; genotype and subtype sequences differ by approximately 30% and 20%, respectively (1, 2). In England, sentinel surveillance data from 2010 to 2014 show GT1 (47%) and GT3 (44%) predominating with other genotypes, including GT4, comprising just 9% of infections (3).

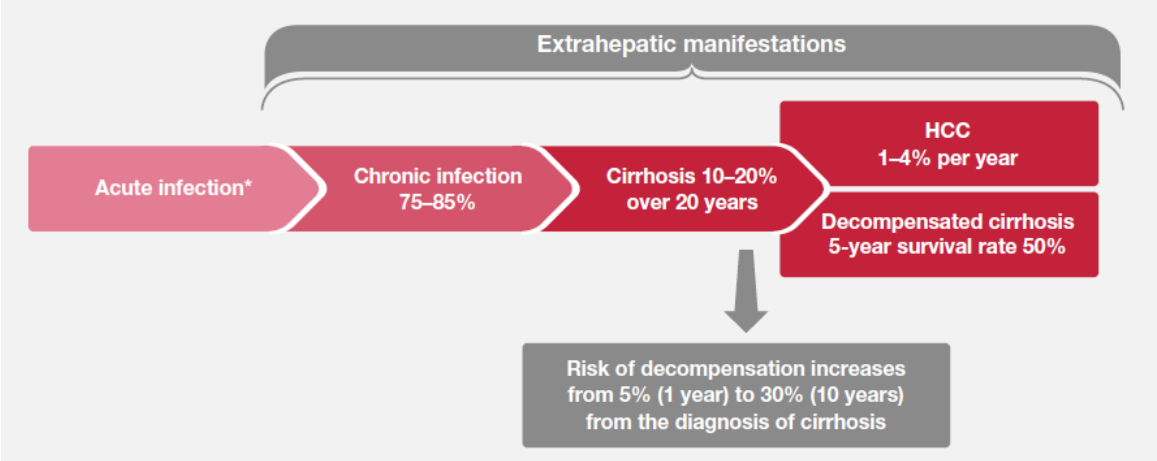
Acute infection is generally asymptomatic and 15–25% of acutely affected individuals will spontaneously clear the virus (1). The remaining 75–85% will go on to develop CHC, defined as persistent, detectable serum HCV RNA for a period greater than 6 months (Figure 1) (1).

Left untreated, patients with CHC are at progressive risk of liver fibrosis, compensated cirrhosis, decompensated cirrhosis, HCC and death (1), as well as extrahepatic diseases including circulatory diseases, renal diseases, autoimmune disorders, cutaneous manifestations and non-liver cancers (4, 5). Progression from compensated to decompensated cirrhosis means that the liver is no longer capable of performing all normal functions and is associated with complications such as ascites, upper gastrointestinal bleeding secondary to varices or portal hypertensive gastropathy, and hepatic encephalopathy (1).

An estimated 10–20% of patients with CHC will go on to develop cirrhosis over a 20-year period and once cirrhosis is established, HCC develops at a rate of 1–4% per year (1). Compensated cirrhosis is associated with a 5-year survival rate of 91%, whereas once decompensated cirrhosis occurs, the 5-year survival rate drops dramatically to 50% (1). HCC is associated with a 1-year survival rate of 67% (2). For patients with decompensated cirrhosis or HCC, a liver transplant is generally required and without a transplant survival prospects are poor (1). CHC is the most common indication for liver transplantation in Europe (42).

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 HBV or HIV (1). HCV genotype has more recently been suggested to impact on the speed of disease progression with GT3 patients being most at risk of rapid progression. Several studies have shown that patients with GT3 infection experience significantly higher rates of fibrosis progression ($p=0.007$) (6), development of HCC ($p=0.003$) (7) and all-cause mortality ($p=0.01$) (8), compared with patients infected with other HCV genotypes. GT3-induced steatosis, which is the accumulation of fat deposits in the liver, has been shown to underlie the accelerated fibrosis observed in GT3 infection (43).

Figure 1: Hepatitis C disease progression



Adapted from Chen and Morgan, 2006 (1).
HCC, hepatocellular carcinoma; HCV, hepatitis C virus.
*20-30% of individuals are symptomatic. Spontaneous clearance of HCV RNA occurs in 15–25% of patients with acute infection.

Progression to cirrhosis is often clinically silent, apart from non-specific symptoms such as fatigue, upper right quadrant pain or, sometimes, arthralgia and myalgia (42). Some patients are not known to have CHC until they present with the complications of end-stage liver disease or HCC (1).

HCV has also been found in sites outside the liver, including bone marrow, the central nervous system, endocrine glands, lymphatic tissue and skin cells. This can result in a host of extrahepatic manifestations, including autoimmune disease, skin reactions, renal injury and neuropathy (42); it is estimated that up to 76% of patients with CHC experience at least one such manifestation (4). These extrahepatic manifestations contribute considerably to the overall disease burden in CHC patients (5).

3.2 *Burden to patients, carers and society*

CHC is associated with considerable burden to patients and society with approximately 214,000 people chronically infected with HCV in the UK currently, including 160,000 people in England (3). The number of laboratory confirmed cases of HCV infection has risen more than 400% over nearly two decades from around 2,000 in 1996 to 11,539 in 2014 (3).

Health burden

As described in Section 3.1 patients are at risk of slowly progressing liver disease, which can result in the serious and life-threatening consequences of cirrhosis, HCC and liver failure, as well as extrahepatic complications (1, 4, 5). The insidious nature of the progression to liver cirrhosis over many years may mean that patients only experience non-specific symptoms until severe complications develop (42).

The incidence of HCV-related liver disease has risen substantially in recent decades, and with transmission among risk groups remaining prominent and significant numbers remaining undiagnosed and untreated (37), this burden is expected to rise still further over the next decade (3). The number of people living with cirrhosis and HCC in England rose by approximately 45% from 7,210 cases in 2005 (37) to 10,470 in 2015 (3), and statistical

modelling suggests this will rise further to 12,510 cases by 2025 if current treatment levels are maintained (3). Similarly, the number of registrations for liver transplants in the UK resulting from hepatitis C-related cirrhosis has increased by almost 300% from 45 cases in 1996 to 175 in 2014 (3). Deaths resulting from HCV-related end-stage liver disease or HCC increased by more than 300% between 1996 and 2014 in England and it is acknowledged that the true number of deaths is likely to be higher (3).

HRQL

CHC is associated with reduced HRQL, becoming evident before the progression to advanced liver disease (44). The main independent predictors of HRQL impairment in untreated patients are fatigue and psychological issues, including depression and anxiety (44). 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 (45). 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 (46).

Healthcare resource burden

Liver disease is estimated to cost the NHS in excess of £500 million per year, a figure that is rising by 10% every year (47).

Overall, there were almost 22,000 recorded hospital admissions for hepatitis C between 2011 and 2012 in England (47); 49% were non-elective, equating to an estimated cost to the NHS of £15–£22 million (47) that could potentially be reduced or avoided with improved awareness, improved diagnosis and treating more patients with effective treatments (47).

Hospital admissions specifically for hepatitis C-related end-stage liver disease and HCC have increased year-on-year in England over the last two decades, rising by more than 350% from 574 in 1998 to 2,652 in 2014 (3).

A liver transplant in the UK is estimated to cost £82,507, with additional costs in the first two years post-transplant estimated at £29,058 (48). This equates to total transplant-related costs alone of around £19.5 million per year based on 175 hepatitis C-related transplants in 2014 (3, 48).

CHC represents a substantial future burden on healthcare resources, as the incidence of serious HCV-related liver disease continues to rise (37). However hepatitis C has been identified as the only type of liver disease for which mortality could be avoided through good quality healthcare (49) and significant progress could be made in a relatively short space of time (47). Further, Public Health England predict that by increasing treatment uptake and introducing more effective DAA treatments rapidly the health and associated healthcare resource burden could be substantially reduced (37). Public Health England recommended that the availability, access and uptake of approved treatment in primary and secondary care, drug treatment services, prisons and other settings needs to be improved (3) so that this could be achieved.

Reducing health and resource use burden through treatment

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 (14). 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 (8, 41, 50-52). In addition, patients experience improved HRQL (44, 53), require reduced healthcare utilisation (54), and importantly, are no longer at risk of transmitting HCV to others.

3.3 *Clinical pathway of care*

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 2015 guidelines (14) and NICE technology appraisals (TA75, 106, 200, 252, 253, 330, 331, 361, 363, 364, and 365) (9-13, 55-60).

Treatment efficacy, and hence decisions around the choice of treatments is multifaceted being influenced by HCV genotype, the severity of liver disease – absence or presence of cirrhosis, and the stage of cirrhosis (compensated or decompensated) – and whether a patient has received treatment for the condition previously – CHC treatment-naïve or treatment-experienced (14).

Historically patients were poorly served with treatments for CHC, with available NICE-recommended regimens limited to Peg-IFN+RBV alone, or the first-generation PIs, BOC and TVR, both taken in combination with Peg-IFN+RBV (9-13).

However, treatment has evolved rapidly since 2014, with multiple new NICE-recommended DAA therapies available, including SOF, LDV/SOF, SMV, DCV, OBV/PTV/RTV, and DSV (55-59). Current NICE recommendations from technology appraisals for CHC treatments are summarised in Table 4 (patients without cirrhosis) and Table 5 (patients with compensated cirrhosis). Based on these recommendations it is clear that some patient groups, such as those with GT1 and GT4 infection are reasonably well served with several treatment choices. However, for other groups such as those with GT3 infection, treatment choices are still limited. Furthermore, the treatment of CHC as a whole has seen a move towards achieving shorter treatment duration, simplifying regimens to cut administration burden, and eliminating the reliance on Peg-IFN and RBV. For some patient groups, such as those with GT3, GT4, GT5 or GT6 infection there is still a reliance on longer treatment duration, and/or Peg-IFN and RBV-containing regimens.

Sofosbuvir/velpatasvir

The FDC of SOF/VEL represents the first pan-genotypic STR for the treatment of CHC, providing a simple, all-oral, once-daily, Peg-IFN- and RBV-free treatment option for all adult patients, including those with compensated cirrhosis. In addition, by adding RBV to the regimen, high cure rates can be achieved in patients with decompensated cirrhosis.

It is anticipated therefore that SOF/VEL will provide a simple, highly effective and well tolerated treatment option for all patients with CHC, irrespective of genotype, severity of liver disease or prior treatment experience. Specifically it will also provide a much-needed option in those groups that are seen to be the hardest to treat and with the highest unmet need, such as those:

- with GT3 infection
- with compensated and decompensated cirrhosis

- who are ineligible for Peg-IFN
- who are ineligible for RBV
- who are CHC treatment-experienced

Details on the current treatment options including related NICE guidance, EASL guidelines and current unmet need are provided in Sections 3.5, 3.6, and 3.7, respectively.

Table 4: Summary of NICE technology appraisal recommendations as of April 2016: for patients with CHC without cirrhosis (includes HCV treatment-naïve and treatment-experienced patients)

GT	SOF+RBV (24, 55)	LDV/SOF (21, 57)	SOF+SMV (60)	SOF+DCV (22, 56)	OBV/PTV/ RTV+DSV (23, 25, 59)	OBV/PTV/ RTV (23, 59)	SOF+P+R (24, 55)	SMV+P+R (26, 58)	DCV+P+R (22, 56)	BOC+P+R (12, 33)	TVR+P+R (13, 32)	P+R (9-11, 15-17)
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
GT1b					**TN/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
GT3	**X**	**X**	**X** (Not licensed)	**TN/TE:** 12w IFN-ineligible only with significant fibrosis	**X** (Not licensed)	**X** (Not licensed)	**TN: X**	**X** (Not licensed)	**X** (Not licensed)	**X** (Not licensed)	**X** (Not licensed)	**TN/TE:** 24w
							TE: 12w					
GT4	**X**	**TN: X**	**X**	**TN:** 12w IFN-ineligible 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
		TE: 12w		**TE:** 12w with significant fibrosis only								
GT5 or 6	**X**	**X**	**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

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; SMV; simeprevir; TE; treatment-experienced; TN; treatment-naïve; TVR, telaprevir; w, weeks.
X denotes that the technology is not recommended; **X** (not licensed) denotes that the technology does not have marketing authorisation for that specific population. Shaded cells represent regimens recommended for a particular HCV genotype.

Table 5: Summary of NICE technology appraisal recommendations as of April 2016: for patients with CHC with compensated cirrhosis (includes HCV treatment-naïve and treatment-experienced patients)

GT	SOF+RBV (24, 55)	LDV/SOF (21, 57)	SOF+SMV (60)	SOF+DCV (22, 56)	OBV/PTV/ RTV+DSV (23, 25, 59)	OBV/PTV/ RTV (23, 59)	SOF+P+R (24, 55)	SMV+P+R (26, 58)	DCV+P+R (22, 56)	BOC+P+R (12, 33)	TVR+P+R (13, 32)	P+R (9-11, 15-17)
GT1a	**X**	**TN:** 12w **TE:** 12w†	**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
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
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
GT4	**X**	**TN:** 12w **TE:** 12w†	**X**	**TN:** 24w +/- RBV IFN-ineligible only **TE:** 24w +/- RBV IFN-ineligible only	**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 12w, REL) or 48w (12w, then P+R 36w (PR/NR)	**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
GT5 or 6	**X**	**X**	**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

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; SMV; simeprevir; TE; treatment-experienced; TN; treatment-naïve; TVR, telaprevir; w, weeks.
X denotes that the technology is not recommended; **X** (not licensed) denotes that the technology does not have marketing authorisation for that specific population. Shaded cells represent regimens recommended for a particular HCV genotype.
† 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.

3.4 *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 (61).

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 three times higher than those expected in the general population (61). Mean age amongst those that died during the study (n=180) was 51.6 years, with an average of 27 years of life lost (61).

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 (62).

Information on prevalence across all indications for SOF/VEL is provided in Section 6.

3.5 *Relevant NICE guidance, pathways or commissioning guides*

Technology appraisals

Recommendations from NICE technology appraisals for each technology appraisal are provided in Table 6. NICE are also currently reviewing grazoprevir-elbasvir [ID842; https://www.nice.org.uk/guidance/indevelopment/gid-ta10032] (anticipated publication date January 2017) in the technology appraisal programme.

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 pending the publication of ongoing technology appraisals for individual treatments for hepatitis C (status last updated 28th January 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 6.

Table 6: NICE technology appraisal guidance in CHC (as of April 2016)

Guidance number/ Issue date	Title	Guidance recommendations (wording as per guidance documents including any reference to other sections in those guidance documents)
TA365/November 2015 (59)	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 genotype 1 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 (56)	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 (57)	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. 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 (60)	Simeprevir in combination with sofosbuvir for treating genotype 1 or 4 chronic hepatitis C	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.

Guidance number/ Issue date	Title	Guidance recommendations (wording as per guidance documents including any reference to other sections in those guidance documents)
	(terminated appraisal)	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 (58)	Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 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 genotype 1 and 4 chronic hepatitis C in adults.
TA330/February 2015 (55)	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 (12)	Boceprevir for the treatment of genotype 1 chronic hepatitis C	1.1 BOC in combination with Peg-IFN alfa and RBV is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease: • Who are previously untreated or • In whom previous treatment has failed.
TA252/April 2012 (13)	Telaprevir for the treatment of genotype 1 chronic hepatitis C	1.1 TVR in combination with Peg-IFN alfa and RBV is recommended as an option for the treatment of genotype 1 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 (11)	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.

Guidance number/ Issue date	Title	Guidance recommendations (wording as per guidance documents including any reference to other sections in those guidance documents)
		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 genotype 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 (10)	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 technology appraisal guidance 75	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 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 (9)	Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C	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:

Guidance number/ Issue date	Title	Guidance recommendations (wording as per guidance documents including any reference to other sections in those guidance documents)
	Partially updated in TA200 This guidance is a review and extension of Technology Appraisal Guidance No. 14 issued in October 2000	• 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 genotype 2 and/or 3 should be treated for 24 weeks. • For people infected with HCV of genotype 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 genotype that includes one or more of genotypes 1, 4, 5, or 6 should be treated as for genotype 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 genotype, 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

Guidance number/ Issue date	Title	Guidance recommendations (wording as per guidance documents including any reference to other sections in those guidance documents)
		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; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; Peg-IFN, pegylated interferon; RBV, ribavirin; TVR, telaprevir.

3.6 *Clinical guidelines*

In addition to the NICE guidance and pathways described in Section 3.5, clinical guidelines and national policies of relevance are listed below:

- EASL Recommendations on Treatment of Hepatitis C 2015 (14)
- 2016 UK consensus guidelines - Treatment Recommendations for the management of patients with Chronic HCV Infection (63)
- NHS England Clinical Commissioning Policy Statement: Treatment of chronic hepatitis C in patients with cirrhosis (64)

EASL Recommendations on Treatment of Hepatitis C 2015 (14), developed by the European Association for the Study of the Liver are the most recent clinical treatment guidelines available, and outline treatment recommendations across all HCV genotypes. Recommendations by genotype are summarised in Table 7 and further summarised in Appendix 2. 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 HCV mono-infected and in HIV co-infected patients without cirrhosis or with compensated (Child-Pugh A) or decompensated (Child-Pugh B or C) cirrhosis, 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 from February 2016 (63) are broadly in line with the EASL guidelines. These guidelines are summarised in Table 8.

NHS England Clinical Commissioning Policy Statement: Treatment of chronic hepatitis C in patients with cirrhosis (64), was published in June 2015, and outlines the hepatitis treatments that would be routinely commissioned by NHS England for the treatment of CHC in patients with cirrhosis. The policy covers compensated and decompensated cirrhosis and includes the following regimens:

- GT1a, compensated cirrhosis:
  - OBV/PTV/RTV+DSV+RBV 12 weeks (not SmPC recommended duration)
  - SMV+Peg-IFN+RBV 12 weeks (followed by Peg-IFN+RBV 12 weeks)
  - LDV/SOF+/-RBV 12 weeks (not SmPC recommended duration/regimen for some cohorts)
- GT1a, decompensated cirrhosis: LDV/SOF+/-RBV 12 weeks (not SmPC recommended duration)
- GT1b, compensated cirrhosis:
  - OBV/PTV/RTV+DSV+RBV 12 weeks
  - SMV+Peg-IFN+RBV 12 weeks (followed by Peg-IFN+RBV 12 weeks)

    - LDV/SOF+/-RBV 12 weeks (not SmPC recommended duration for some cohorts)
- GT1b, decompensated cirrhosis: LDV/SOF+/-RBV 12 weeks (not SmPC recommended duration)
- GT3, compensated cirrhosis
    - SOF+Peg-IFN+RBV 12 weeks (if likely to be IFN-tolerant)
    - SOF+DCV+RBV 12 weeks (if IFN contraindicated; not SmPC recommended duration)
    - LDV/SOF+/-RBV 12 weeks (if IFN contraindicated; not SmPC recommended duration)
- GT3, decompensated cirrhosis:
    - SOF+DCV+RBV 12 weeks (not SmPC recommended duration)
    - SOF/LDV+RBV 12 weeks (not SmPC recommended duration)
- GT4, compensated cirrhosis:
    - SMV+Peg-IFN+/-RBV 12 weeks (followed by Peg-IFN+RBV 12 weeks)
    - LDV/SOF 12 weeks (not SmPC recommended duration/regimen for some cohorts)
- GT4, compensated cirrhosis:
    - LDV/SOF+/-RBV 12 weeks (not SmPC recommended duration).

Table 7: Summary of EASL recommendations for CHC

Genotype	Regimen	Recommendation
GT1	SOF+P+R (12 weeks)	IFN-containing option 1
	SMV+P+R (12 weeks), followed by P+R for an additional 12 or 36 weeks	IFN-containing option 2 • Not recommended in patients infected with subtype 1a who have detectable Q80K substitution in the NS3 protease sequence at baseline • P+R for an additional 12 weeks (total treatment duration 24 weeks) in TN and prior relapser patients, including cirrhotic patients, and for an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotic patients
	LDV/SOF (12 weeks)	IFN-free option 1 • Patients without cirrhosis (TN or TE) should be treated for 12 weeks • For TN patients without cirrhosis treatment may be shortened to 8 weeks if baseline HCV RNA level <6 million IU/mL • For patients with compensated cirrhosis, including TN and TE patients, treat with LDV/SOF+RBV for 12 weeks • For patients with compensated cirrhosis with contraindications to/poor tolerance to RBV treat for 24 weeks without RBV • Treatment with LDV/SOF+RBV can be prolonged to 24 weeks in TE patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 x 10^3/µL
	OBV/PTV/RTV+DSV (12 weeks)	IFN-free option 2 • For patients with GT1b without cirrhosis • For patients with GT1b with cirrhosis or GT1a without cirrhosis add RBV • For patients with GT1a with cirrhosis add RBV and treat for 24 weeks
	SOF+SMV (12 weeks)	IFN-free option 3 • For patients with compensated cirrhosis add RBV • For patients with cirrhosis with contraindications to RBV, consider extending duration to 24 weeks
	SOF+DCV (12 weeks)	IFN-free option 4 • For patients with compensated cirrhosis add RBV • For patients with cirrhosis with contraindications to RBV, consider extending duration to 24 weeks
GT2	SOF+RBV (12 weeks)	Option 1

Genotype	Regimen	Recommendation
		• For patients with cirrhosis or if TE extend to 16–20 weeks
	SOF+P+R (12 weeks)	Option 2 • Option for cirrhotic and/or TE patients
	SOF+DCV (12 weeks)	Option 3 • Option for cirrhotic and/or TE patients
GT3	SOF+P+R (12 weeks)	Option 1 • This combination is valuable for patients who failed to achieve SVR after SOF+RBV
	SOF+RBV (24 weeks)	Option 2 • Suboptimal in TE cirrhotic patients and those who failed to achieve SVR after SOF+RBV
	SOF+DCV (12 weeks)	Option 3 • For TN and TE patients without cirrhosis • For TN and TE patients with cirrhosis add RBV and treat for 24 weeks
GT4	SOF+P+R (12 weeks)	IFN-containing option 1
	SMV+P+R (12 weeks) followed by P+R for an additional 12 or 36 weeks	IFN-containing option 2 P+R for additional 12 weeks (total treatment duration 24 weeks) in TN and prior relapser patients, including cirrhotic patients, and for additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotic patients
	LDV/SOF (12 weeks)	IFN-free option 1 • Patients without cirrhosis (TN or TE) should be treated for 12 weeks • For patients with compensated cirrhosis, including TN and TE patients, treat with LDV/SOF+RBV for 12 weeks • For patients with compensated cirrhosis with contraindications to/poor tolerance to RBV treat for 24 weeks without RBV • Treatment with LDV/SOF+RBV can be prolonged to 24 weeks in TE patients with compensated cirrhosis and negative predictors of response, such as a platelet count $<75 \times 10^3/\mu L$
	OBV/PTV/RTV+RBV (12–24 weeks)	IFN-free option 2 • For patients without cirrhosis treat for 12 weeks • For patients with cirrhosis treat for 24 weeks

Genotype	Regimen	Recommendation
	SOF+SMV (12 weeks)	IFN-free option 3 • For patients with cirrhosis add RBV • For patients with cirrhosis with contraindications to RBV, extend duration to 24 weeks
	SOF+DCV (12 weeks)	IFN-free option 4 • For patients with cirrhosis add RBV • For patients with cirrhosis with contraindications to RBV, extend duration to 24 weeks
GT5 or 6	SOF+P+R (12 weeks)	Option 1
	LDV/SOF (12 weeks)	Option 2 • Patients without cirrhosis (TN or TE) should be treated for 12 weeks • For patients with compensated cirrhosis, including TN and TE patients, treat with LDV/SOF+RBV for 12 weeks • For patients with compensated cirrhosis with contraindications to/poor tolerance to RBV treat for 24 weeks without RBV • Treatment with LDV/SOF+RBV can be prolonged to 24 weeks in TE patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 x 10^3/µL
	SOF+DCV (12 weeks)	Option 3 • For patients with cirrhosis, add RBV • For patients with cirrhosis with contraindications to RBV, extend duration to 24 weeks

DCV; daclatasvir; DSV, dasabuvir; EASL; European Association for the Study of the Liver; FDC; fixed dose combination; HCV; hepatitis C virus; IU; international units; LDV; ledipasvir; OBV; ombitasvir; P; pegylated interferon; PTV; paritaprevir; R or RBV; ribavirin; RNA; ribonucleic acid; RTV; ritonavir; SMV; simeprevir; SOF, sofosbuvir; SVR; sustained virological response; TE; treatment-experienced; TN; treatment-naïve.
Source: EASL recommendations on treatment of hepatitis C 2015 (14).

Table 8: Summary of UK consensus guidelines treatment options for CHC

Genotype	Non-cirrhotic	Cirrhotic
GT1 TN	• SOF/LDV (8 weeks) • GT1a only: OBV/PTV/RTV+DSV+RBV (12 weeks) • GT1b only: OBV/PTV/RTV+DSV (12 weeks)	• SOF/LDV±RBV (12 weeks)[†] • Child Pugh A only: OBV/PTV/RTV+DSV+RBV (12 weeks)[‡§]

Genotype	Non-cirrhotic	Cirrhotic
GT1 TE	• SOF/LDV (12 weeks) • GT1a only: OBV/PTV/RTV+DSV+RBV (12 weeks) • GT1b only: OBV/PTV/RTV+DSV (12 weeks)	• SOF/LDV±RBV (12 weeks)[†] • Child Pugh A only: OBV/PTV/RTV+DSV+RBV (12/24 weeks)[§]
	• Should SOF/VEL or elbasvir/grazoprevir become available during the lifetime of these recommendations, the Operational Delivery Networks would encourage NHS England to make these drugs available within their licensed indications	
GT2 TN	• Peg-IFN+RBV (24 weeks; 12-16 weeks in patients with high chance of good response) • IFN intolerant: SOF+RBV (12 weeks)	• Peg-IFN+RBV (24 weeks) • IFN intolerant: SOF+RBV (12 weeks)
GT2 TE	• SOF+RBV (12 weeks)	• SOF+RBV (12 weeks)
	• The panel recommends that NHSE be asked to support a policy of SOF+Peg-IFN+RBV for IFN sensitive patients with advanced fibrosis (F3) or cirrhosis • Should SOF/VEL become available during the lifetime of these recommendations, the Operational Delivery Networks would encourage NHS England to make these drugs available within their licensed indications	
GT3 TN	• <F3: Peg-IFN+RBV 24 wks OR Consider waiting for new therapies[††] • F3: Peg-IFN+RBV 24 wks • F3 IFN intolerant: SOF+DCV±RBV (12 weeks)[¶] • OR Consider waiting for new therapies[††]	• SOF+Peg-IFN+RBV (12 weeks) • IFN intolerant: SOF+DCV±RBV (12 weeks)[¶]
GT3 TE	• <F3: SOF+Peg-IFN+RBV OR Consider waiting for new therapies[††] • F3: SOF+Peg-IFN+RBV (12 weeks) • F3 IFN intolerant: SOF+DCV±RBV (12 weeks)[¶]	• SOF+Peg-IFN+RBV (12 weeks) • IFN intolerant: SOF+DCV±RBV (12 weeks)[¶]
	• The clinicians have recommended that NHSE consider funding SOF+Peg-IFN+RBV for patients with F3 fibrosis • Should SOF/VEL become available during the lifetime of these recommendations, the Operational Delivery Networks would encourage NHS England to make these drugs available within their licensed indications	
GT4 TN	• OBV/PTV/RTV±RBV (12 weeks)[‡‡]	• SOF/LDV (12 weeks) • OBV/PTV/RTV+RBV (12 weeks)
GT4 TE	• SOF/LDV (12 weeks) • OBV/PTV/RTV+RBV (12 weeks)	• SOF/LDV±RBV (12 weeks) • OBV/PTV/RTV+RBV (24 weeks)[§§]

Genotype	Non-cirrhotic	Cirrhotic
	• Should SOF/VEL or elbasvir/grazoprevir become available during the lifetime of these recommendations, the Operational Delivery Networks would encourage NHS England to make these drugs available within their licensed indications	
GT5/6	• Insufficient data to develop a consensus at this time • For IFN tolerant patients SOF+Peg-IFN+RBV should be made available • For IFN intolerant patients we recommend that SOF/LDV be provided • In the future if SOF/VEL is available we suggest that NHSE consider making this drug available for these patients	
DCC	• GT1, GT2, GT4: If treated during decompensation then SOF/LDV+RBV (12 weeks) is appropriate • GT3: If treated during decompensation then SOF+DCV+RBV (12 weeks) is appropriate	
HIV co-infection	• In general, the same DAA-based regimens used in HCV mono-infection are applicable to co-infected patients with chronic HCV	

DCC, decompensated cirrhosis; DCV; daclatasvir; DSV, dasabuvir; LDV; ledipasvir; OBV; ombitasvir; Peg-IFN; pegylated interferon; PTV; paritaprevir; RBV; ribavirin; RTV; ritonavir; SMV; simeprevir; SOF, sofosbuvir; TE; treatment-experienced; TN; treatment-naïve.
Source: UK Consensus Guidelines (63). † Consider RBV in patients more likely to have a poor response (e.g. prior null responders); ‡ In patients at low risk of treatment failure RBV may be omitted; § 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); †† 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; ‡‡ In exceptional circumstances, can consider SOF+DCV+RBV or SOF/LDV 12 weeks (Not NICE approved), in those patients in whom drug-drug interactions with OBV/PTV/RTV+RBV are considered a potential concern; §§ For patients who are at low risk of treatment failure consideration should be given to 12 weeks treatment.

3.7 *Issues relating to current clinical practice*

IFN-based regimens have formed the cornerstone of CHC treatment for the last two decades (18) and until recently individuals would have been prescribed either dual therapy with Peg-IFN+RBV or triple therapy with first generation PIs (BOC or TVR), combined with Peg-IFN+RBV.

However, Peg-IFN and RBV are associated with several limitations including:

- SVR rates as low as 40–50% with Peg-IFN+RBV in patients infected with HCV GT1 (14).
- Significant side effect profiles including:
    - Influenza-like symptoms, fatigue, psychiatric disorders, skin reactions and haematological events for Peg-IFN+RBV used in combination (14).
    - When used in IFN-free regimens the most important side effects with RBV include haemolytic anaemia, which can result in deterioration of cardiac function and/or worsening of pre-existing cardiac disease, and due to significant teratogenic and/or embryocidal effects seen in animals, the potential for birth defects. This means that RBV should not be used by women during pregnancy or in male partners of women who are pregnant (14, 15). Furthermore, women of childbearing potential must use effective contraception during treatment and for 4 months after its completion, due to the prolonged risk of birth defects due to the long half-life (15). In male patients with female partners of childbearing potential, this risk period and requirement for use of an effective contraception extends to 7 months after treatment, with routine monthly pregnancy tests for their partner during this time.
- Contraindicated in a number of patient groups, including those with autoimmune hepatitis (Peg-IFN), severe hepatic dysfunction or decompensated cirrhosis (Peg-IFN), history of pre-existing cardiac disease (Peg-IFN and RBV), blood disorders such as thalassaemia or sickle cell anaemia (RBV) or women who are pregnant or breast feeding (RBV) (15-17).
- The need for safety and efficacy monitoring and support (Peg-IFN+RBV and RBV alone) (14, 18).
- High discontinuation rates due to AEs (11% discontinued Peg-IFN+RBV treatment in a clinical trial setting (19)).
- Long duration of treatment (up to 48 weeks for Peg-IFN+RBV) (16, 17)
- Weekly subcutaneous injections (Peg-IFN) (16, 17) or multiple tablets daily (RBV) (15).

As such, CHC therapy with Peg-IFN-based regimens proves difficult for some patients, and limits the proportion that start or complete therapy (18). [redacted] (20).

EASL now recommends that IFN-free regimens, when available, provide the best option for all patients (14), and the emergence of DAA therapies has provided treatment options for most patients that are generally easier to take and are more tolerable.

The introduction of the first DAAs, the PIs TVR and BOC provided patients infected with GT1 with an improved chance of a cure compared with Peg-IFN+RBV (14), and in some patients

resulted in shortened treatment duration (32, 33). However, a significant proportion of patients who have failed therapy with Peg-IFN+RBV also fail PI-based triple therapy (65–85% in prior null or partial responders with cirrhosis), making this a key unmet clinical need (65).

Other considerations of first generation PI-based triple therapy included the following: only licensed for use in patients with HCV GT1 infection (32, 33); the requirement for Peg-IFN (32, 33); an increase in some side effects compared with Peg-IFN+RBV dual therapy (66); high pill burden and up to thrice daily dosing (32, 33); clinically significant drug interactions (67); emergence of drug-resistant variants (68).

The CHC treatment landscape has subsequently evolved dramatically to address these limitations and since 2014, multiple DAA-based regimens have come to market and achieved positive NICE recommendations. These include SMV, a second generation PI, and various individual drugs or FDCs which target inhibition of non-structural viral protein NS5A and/or viral NS5B polymerase, including SOF, LDV/SOF, DCV, OBV/PTV/RTV, and DSV (55-59).

The evolution of the CHC treatment landscape beyond Peg-IFN+RBV and the first generation PIs has seen a move towards improved tolerability, shorter treatment duration, simplified regimens to cut administration burden, and eliminating the reliance on Peg-IFN and RBV.

Some of the current NICE-recommended DAA-based regimens provide simpler, short duration, RBV-free regimens, with up to 100% SVR rates for non-cirrhotic GT1 patients (21-24).

However, there is still a reliance on RBV, and in some cases Peg-IFN, or longer treatment durations to achieve high (≥90%) SVR rates in GT2–6 patients, GT1 cirrhotic patients and other difficult to treat subgroups, such as those with decompensated cirrhosis in whom Peg-IFN cannot be used (21-24). In particular GT3 treatment-naïve non-cirrhotic patients do not currently have access to any regimens which demonstrate high (>90%) efficacy, and in fact do not have access to any DAA-based option, relying only on Peg-IFN+RBV.

Furthermore, first generation PIs (BOC and TVR) are limited by the high risk of resistance development following treatment failure (in 50–75% of patients not achieving an SVR, and in 90% of those with virologic failure) which could impact on the success of subsequent therapy (68). The development of resistance is still an issue, with SMV requiring baseline screening of patients being considered for treatment (68).

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 (22, 23, 25, 26).

Therefore, despite the advances in the treatment of CHC, there still remains substantial unmet need for simple, short duration, RBV- and Peg-IFN-free, highly effective, pan-genotypic and well tolerated therapies. Groups that are still of particular concern are those for whom high SVR rates are more difficult to achieve and thus are considered more difficult to treat. These patients groups include those:

- with compensated and decompensated cirrhosis
- who are ineligible for Peg-IFN
- who are ineligible for RBV
- who are CHC treatment-experienced

- with GT3 infection

GT3 CHC

The population with chronic GT3 infection arguably represents the population of greatest unmet clinical need, because of the size and additional morbidity associated with this particular HCV genotype. GT3 accounts for around 44% of all HCV infections in England (3). Furthermore, several studies have shown that patients with GT3 infection experience significantly higher rates of fibrosis progression (p=0.007) (6), development of HCC (p=0.003) (7) and all-cause mortality (p=0.01) (8), compared with patients infected with other HCV genotypes.

In spite of this, and the recent advances in treatment regimens for other genotypes, there are still very limited NICE-recommended DAA-based options available for GT3, and for some there is no DAA-based option at all, leaving only Peg-IFN+RBV or no treatment as the viable options. Treatment outcomes for GT3 patients treated with Peg-IFN+RBV are poor, with real-world data in England showing [redacted](20).

- For ***GT3 treatment-naïve patients***, SOF+DCV is limited to IFN-ineligible patients with significant fibrosis or those with cirrhosis, SOF+Peg-IFN+RBV is limited to those with cirrhosis, and SOF+RBV is limited to IFN-ineligible patients with cirrhosis (Table 4 and Table 5, (55, 56).
    - As such, ***treatment-naïve patients without cirrhosis*** are extremely poorly served with the majority of patients having no access to a DAA-based option, and SOF+DCV, the only DAA recommended by NICE, being limited to patients who are ineligible for IFN and have significant fibrosis (Table 4, (56).
- For ***GT3 treatment-experienced patients***, the only DAA-based regimen available for all is SOF+Peg-IFN+RBV, with other DAAs (SOF+RBV and SOF+DCV) again limited by IFN ineligibility or cirrhotic status (Table 4 and Table 5, (55, 56).

SOF/VEL will provide a simple, highly effective and well tolerated treatment option for all patients with CHC, irrespective of genotype, severity of liver disease or prior treatment experience. Specifically it will also provide a much-needed option in those groups that are seen to be the hardest to treat and with the highest unmet need, such as those with GT3 infection, the majority of whom do not have access to an all-oral CHC treatment at the present time.

3.8 *Equality*

[redacted] This could potentially raise an equality issue if these people encounter greater difficulty in achieving access to SOF/VEL.

In addition, access to an effective treatment like SOF/VEL would change the distribution and the dynamic of the CHC infected population in the UK, and particularly GT3, which is highly prevalent. The treatment landscape in GT1 infection has drastically improved in recent years, with a number of new treatments with very high SVR rates being recommended by NICE. While SOF/VEL is a pan-genotypic regimen offering high efficacy across all genotypes, the value of SOF/VEL is particularly pronounced in the context of GT3 infection, where limited treatment options are available and in some case (for example, in GT3 treatment-naïve non-cirrhotic

patients), no DAA is available. Therefore access to SOF/VEL would enable all CHC patients to receive a highly effective and tolerable treatment, including those patient populations characterised by a disproportionate prevalence of people from migrant backgrounds.

4 Clinical effectiveness

4.1 *Identification and selection of relevant studies*

A systematic review was conducted to retrieve relevant randomised clinical data from the published literature regarding the efficacy of SOF/VEL and comparators of relevance to the NICE decision problem.

4.1.1 *Search strategy*

Searches were conducted in the following electronic databases on 17th December 2015:

- MEDLINE® and MEDLINE® In-Process (Ovid SP®)
- EMBASE (Ovid SP®)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- PubMed (to identify e-Pubs ahead of print)

The search strategies combined free text and controlled vocabulary terms (MeSH in MEDLINE® and CENTRAL, and EMTREE terms in EMBASE). Search filters to identify RCTs were used in MEDLINE® and EMBASE (from the Cochrane Handbook and the Cochrane Renal group, respectively).

Database searches were supplemented by searching the following conference sources from 2014 and 2015 (search conducted 15th January 2016):

- European Association for the Study of the Liver (EASL)
- The Liver Meeting (AASLD)

Both conferences were searchable through EMBASE and thus a search strategy similar to that used to identify full publications was used.

Full details of the search are provided in Appendix 3.

4.1.2 *Study selection*

Study selection was conducted according to the eligibility criteria outlined in Table 9 (defined according to the PICOS statement (patients, interventions, comparators, outcomes, study design). Eligibility criteria apply for all studies whether full papers or conference abstracts. Study selection was restricted to English language publications.

At full paper review stage, papers describing studies in Asian or Egyptian patients were excluded as those populations were deemed not to be the focus of this review and because recommended treatments differ in these regions.

At full paper review stage, the dosing strategies of the treatment arms were assessed. Only doses that are currently licenced, or expected to be licenced were included. The doses included in the review are listed in Table 10. In publications where more than one dosing regimen is reported, only the licenced dosing regimen was extracted.

Table 9: Eligibility criteria used in search strategy

PICOS	Inclusion criteria
Population	Adult patients infected by HCV with genotypes 1–6 HCV, treatment-naïve or treatment-experienced, HIV co-infected, recurrent HCV, liver transplant patients
Interventions and comparators	• Pegylated interferon alpha, ribavirin, telaprevir, boceprevir, simeprevir, daclatasvir, asunaprevir,† sofosbuvir, faldaprevir,† ledipasvir, ombitasvir, paritaprevir, ritonavir, dasabuvir, grazoprevir, elbasvir, velpatasvir, placebo, no treatment • Only combinations with and comparisons between list drugs were included • Only licenced doses, or doses expected to be licenced, were included
Outcomes	SVR12/24, RVR, EVR, eRVR, EOT, safety outcomes and mortality
Study design	Randomised trials: Phase II and III clinical trials

EOT, end of treatment; eRVR, extended rapid virologic response; EVR, early virologic response; RVR, rapid virologic response; SVR, sustained virologic response.
†These comparators were included in the initial protocol but subsequently removed at full paper review stage as marketing authorisation applications for these products is not being pursued in this indication.
eRVR defined as undetectable HCV RNA levels at weeks 4 and 12 of treatment; EVR defined as undetectable HCV RNA level at week 12 of treatment; RVR defined as undetectable HCV RNA level at week 4 of treatment; SVR12/24 defined as undetectable serum HCV RNA 12/24 weeks after the end of treatment.

Table 10: Study treatment doses included

Treatment	Dose
Boceprevir	2,400 mg OD
Daclatasvir dihydrochloride	60 mg OD
Dasabuvir sodium	500 mg OD
Ombitasvir/paritaprevir/ritonavir	25 mg/150 mg/ 100 mg OD
Peginterferon alpha-2a	180 µg (once weekly)
Peginterferon alpha-2b	Weight based (1.5 µg/kg/week)
Ribavirin	Weight based (800–1,400 mg)
Simeprevir	150 mg OD
Sofosbuvir	400 mg OD
Sofosbuvir/ledipasvir	400 mg/90 mg OD
Telaprevir	2,250 mg OD
Velpatasvir	100 mg OD

OD, once daily.

A total of 4,986 abstracts were identified after removal of duplicates and 224 were subsequently reviewed as full papers. Following full paper-review, 89 publications (reporting on 92 studies) were identified as meeting the eligibility criteria. Another 10 abstracts were identified from conference proceedings (eight additional studies plus one study reported in a full publication).

Of these, six publications/conference abstracts (reporting on seven studies) included treatment arms incorporating SOF/VEL (28, 70-74).

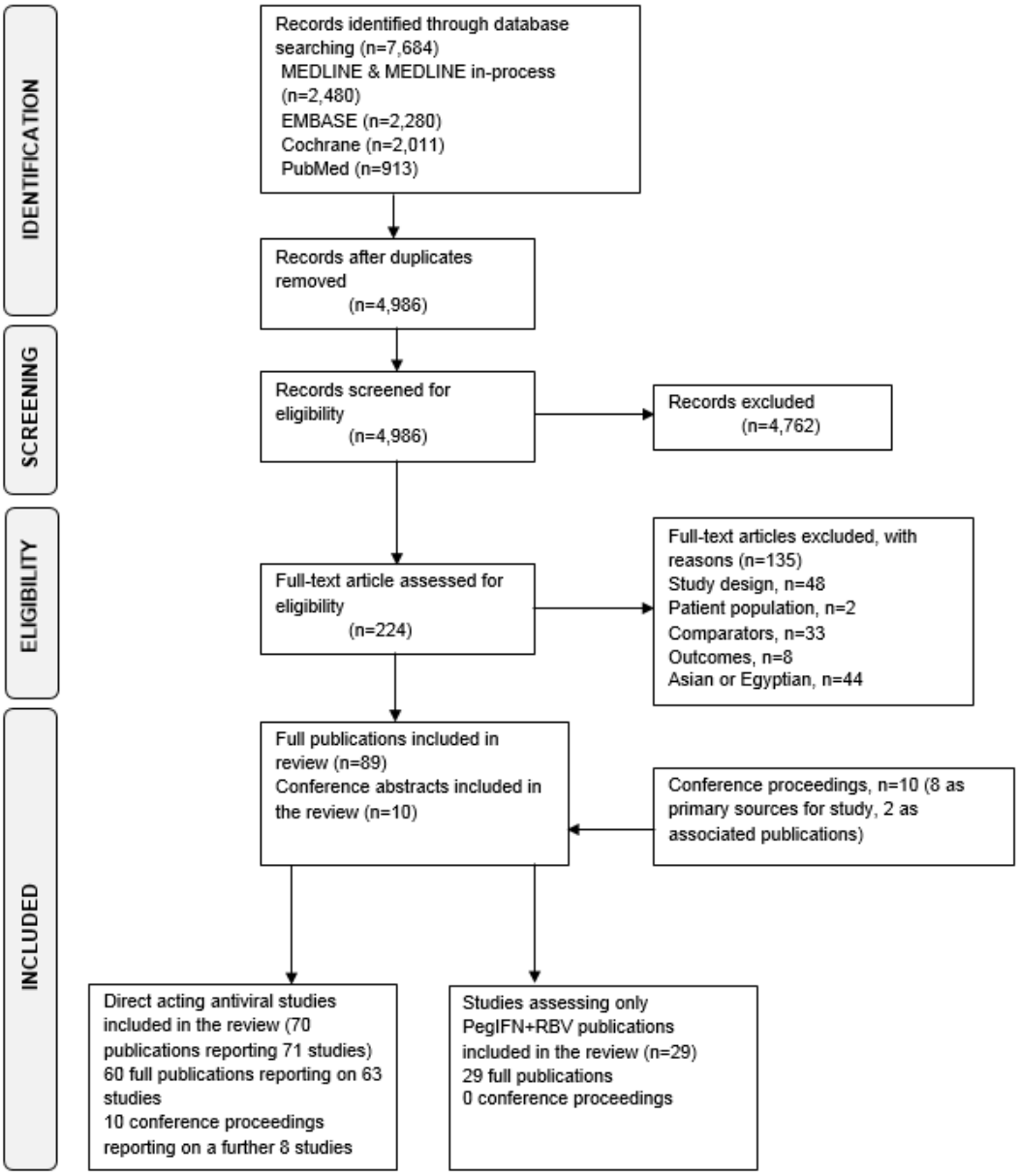
- ASTRAL-1, ASTRAL-2 and ASTRAL-3 (28, 70) are the pivotal RCTs and are listed in Section 4.2.

- ASTRAL-4, ELECTRON-2, Everson et al, 2015 and Pianko et al, 2015 (71-74) are randomised, non-controlled studies and are discussed in Section 4.10.9.1.

The remaining publications provide comparator data, based on the interventions listed in Table 9, and are discussed in Section 4.10.

The systematic review schematic is shown in Figure 2.

Figure 2: Schematic for the systematic review of clinical evidence



A full list of excluded studies is provided in Appendix 3.

4.2 *List of relevant randomised controlled trials*

The original Phase III clinical trial program for SOF/VEL included two RCTs – one in patients with HCV GT1, GT2, GT4, GT5, or GT6 (ASTRAL-1) and one in patients with HCV GT3 (ASTRAL-3). A separate trial with an active comparator group was deemed to be necessary for patients with HCV GT3 in light of specific clinical challenges presented in this population. After the protocol for ASTRAL-1 was finalised and trial activity had been initiated, the FDA in the US requested a separate trial with an active comparator for patients with HCV GT2. Because enrolment in ASTRAL-1 had already begun, the trial protocol was not amended to exclude patients infected with HCV GT2. Therefore, two additional Phase III RCTs were conducted to evaluate SOF/VEL in patients with HCV GT2 (ASTRAL-2) and HCV GT3 (ASTRAL-3).

The ASTRAL RCTs all enrolled adult patients with CHC who could be HCV treatment-naïve or treatment-experienced, and included those with compensated cirrhosis.

- ASTRAL-3 provides comparative evidence versus active treatment (SOF+RBV 24 weeks) for the use of SOF/VEL for 12 weeks in patients with HCV GT3 infection, a key population with high unmet need and the focal population of this submission.
- ASTRAL-2 provides comparative evidence versus active treatment (SOF+RBV 12 weeks) for the use of SOF/VEL for 12 weeks in patients with HCV GT2 infection, using identical methodology to that employed for ASTRAL-3.
- ASTRAL-1 provides comparative evidence versus placebo for the use of SOF/VEL for 12 weeks in patients with HCV GT1, GT2, GT4, GT5, and GT6 infection, with similar methodology to that employed in ASTRAL-2 and -3.

Throughout this section, information from these three trials is presented in the following order: ASTRAL-3; ASTRAL-2; ASTRAL-1.

The ASTRAL trials are briefly summarised in Table 11 and described in detail in Sections 4.3 through 4.8.

Table 11: List of relevant RCTs

Trial no. (acronym)	Intervention(s)	Comparator(s)	Population	Primary study refs.
Pivotal Phase III RCTs				
GS-US-342-1140 (ASTRAL-3)	• SOF/VEL for 12 weeks	• SOF+RBV for 24 weeks	• CHC GT3 • Treatment-naïve and treatment-experienced • No cirrhosis and compensated cirrhosis	Foster et al, 2015 (28) Supporting information from CSR (75)
GS-US-342-1139 (ASTRAL-2)	• SOF/VEL for 12 weeks	• SOF+RBV for 12 weeks	• CHC GT2 • Treatment-naïve and treatment-experienced • No cirrhosis and compensated cirrhosis	Foster et al, 2015 (28) Supporting information from CSR (76)
GS-US-342-1138 (ASTRAL-1)	• SOF/VEL for 12 weeks	• Placebo for 12 weeks	• CHC GT1, GT2, GT4, GT5, GT6 • Treatment-naïve and treatment-experienced • No cirrhosis and compensated cirrhosis	Feld et al, 2015 (70) Supporting information from CSR (77)

CHC, chronic hepatitis C; CSR, clinical study report; GT, genotype; RBV, ribavirin; RCT, randomised controlled trial; SOF, sofosbuvir; VEL, velpatasvir.

4.3 *Summary of methodology of the relevant randomised controlled trials*

4.3.1 *Comparative summary of RCT methodology*

The methodologies of the ASTRAL RCTs are summarised in Table 12.

Table 12: Comparative summary of methodology

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
Study objective	• To compare the efficacy of treatment with SOF/VEL for 12 weeks with that of SOF+RBV for 24 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 for 12 weeks with that of SOF+RBV for 12 weeks as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of each treatment regimen	• To evaluate the efficacy of treatment with SOF/VEL for 12 weeks in patients with CHC as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of treatment with SOF/VEL for 12 weeks
Location	76 sites in the United States, Canada, Europe (France, Germany, Italy, and the United Kingdom), Australia, and New Zealand. 11 sites (105 patients) in the United Kingdom.	51 sites in the United States.	81 sites in the United States, Canada, Europe (France, Germany, Belgium, Italy and the United Kingdom), and Hong Kong. 11 sites (104 patients) in the United Kingdom.
Design	Multicentre, randomised, open-label, active controlled, Phase III.		Multicentre, randomised, double-blind, placebo-controlled, Phase III.
Duration of study	Treatment duration: 12 or 24 weeks depending on treatment assignment. Follow-up: up to 24 weeks.	Treatment duration: 12 weeks. Follow-up: up to 24 weeks.	Treatment duration: 12 weeks. Follow-up: up to 24 weeks.
Method of randomisation	An IWRS was employed to manage patient randomisation and treatment assignment. Randomisation was stratified by: • Cirrhosis status (Presence or absence of cirrhosis) • Prior treatment experience (treatment-naïve or treatment-experienced)		An IWRS was employed to manage patient randomisation and treatment assignment. Randomisation was stratified by: • Cirrhosis status (Presence or absence of cirrhosis) • Genotype (1, 2, 4, 6, indeterminate)
Method of blinding (care	The study was open-label. All investigators, patients, and trial personnel were aware of the treatment assignments at all points.		The study was double-blinded. Study drugs were dispensed to patients in a blinded fashion as

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
provider, patient and outcome assessor)			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 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 must have been clearly explained in source documentation and on the electronic case report form, 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 patient's treatment assignment was disclosed to the investigator, study treatment was discontinued for the patient.
Intervention(s) (n=) and comparator(s) (n=)	Patients were randomised in a 1:1 ratio to: • SOF/VEL for 12 weeks (n=277) • SOF+RBV for 24 weeks (n=275) Patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily, or 400 mg of SOF once daily plus RBV. RBV was administered orally twice daily, with the dose determined according to body weight (1,000 mg daily in patients with a body weight <75 kg, and 1,200 mg daily in patients with a body weight	Patients were randomised in a 1:1 ratio to: • SOF/VEL for 12 weeks (n=135) • SOF+RBV for 12 weeks (n=134) Patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily, or 400 mg of SOF once daily plus RBV. RBV was administered orally twice daily, with the dose determined according to body weight (1,000 mg daily in patients with a body weight <75 kg, and 1,200 mg daily in	**Patients infected with HCV GT1, GT2, GT4 or GT6:** Randomised 5:1 to: • SOF/VEL for 12 weeks (n=590) • Placebo for 12 weeks (n=116) Patients in the placebo group were eligible for deferred treatment with SOF/VEL for 12 weeks. **Patients infected with HCV GT5:** Given the low prevalence of HCV GT5 infection, enrolment of only 20 patients was targeted for this

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
	≥75kg).	patients with a body weight ≥75kg).	group and 35 were eventually enrolled. These patients did not undergo randomisation and were pre-specified to receive SOF/VEL for 12 weeks. Patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily, or a placebo tablet to match the active treatment once daily.
Permitted and disallowed concomitant medications	Concomitant medications taken within 30 days of screening, up to and including 30 days after the last dose of study drug, were recorded. The following were prohibited from 28 days prior to the baseline/Day 1 visit through the EOT visit: • Haematologic stimulating agents (e.g. ESAs, GCSF, TPO mimetics) • Chronic systemic immunosuppressants including: ○ Corticosteroids (prednisone equivalent of >10 mg/day for >2 weeks) ○ Azathioprine ○ Monoclonal antibodies (e.g. infliximab) • Investigational agents or devices for any indication • Drugs disallowed according to prescribing information of SOF or RBV ***(ASTRAL-2 and ASTRAL-3 only)*** Concomitant use of medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e. P-glycoprotein) which may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug(s) or these medications. Examples of representative medications that were prohibited from 21 days prior to baseline/Day 1 through EOT are listed in the clinical study protocol. Medications for disease conditions excluded from the protocol (e.g., HIV-1, active cancer, transplantation) were not listed as concomitant medications and were disallowed in the study.		
Assessments performed	• All patients were to have study visits at screening, baseline, and on-treatment at the end of week 1, 2, 4, 6, 8, 10 and 12 • ASTRAL-2 only: patients in the SOF+RBV arm had additional on-treatment visits at the end of week 16, 20 and 24 • Post-treatment visits were to occur at week 4, 12 and 24 (if applicable) • Screening assessments were to be completed within 28 days (42 days if liver biopsy or additional HCV genotype testing required) of the baseline/Day 1 visit • All patients had to complete post-treatment week 4 and week 12 assessments, regardless of treatment duration. Patients with HCV RNA <LLOQ at post-treatment week 12 had to complete post-treatment week 24 assessments, unless confirmed viral relapse occurred **Assessments included:**		

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
	• Complete physical examination (screening, baseline, week 12) ○ On-treatment week 24 (SOF+RBV arm only, ***ASTRAL-3 only***) • Body weight (screening, baseline, week 12, post-treatment weeks 12 and 24) ○ On-treatment week 24 (SOF+RBV arm only, ***ASTRAL-3 only***) • Vital signs† (every visit) • 12-lead ECG (screening, baseline, weeks 1 and 12) • AEs and concomitant medications (every visit) • Serum HCV RNA (every visit) • IL28B genotyping (screening) • Viral RNA sequencing and phenotyping (every visit except screening) • HCV genotype and subtype (screening only) • HRQL surveys (baseline, weeks 4, 8 and 12, post-treatment weeks 4, 12 and 24) ○ On-treatment week 24 (SOF+RBV arm only, ***ASTRAL-3 only***)		
Primary outcomes (including scoring methods and timings of assessments)	SVR12, defined as HCV RNA <LLOQ, 12 weeks after the end of treatment, in the FAS population. The LLOQ was 15 IU/mL.		
Secondary outcomes (including scoring methods and timings of assessments)	• Proportion of patients with SVR (HCV RNA<LLOQ) at 4 weeks and 24 weeks after end of treatment (SVR4 and SVR24) • The proportion of patients with HCV RNA<LLOQ on treatment by study visit • HCV RNA change 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 • Characterisation of drug resistance at baseline, during and after therapy: Deep sequencing of the HCV NS5A and NS5B coding regions was performed on samples obtained from all patients at baseline and again for all patients with virologic failure. Sequences that were obtained at the time of virologic failure were compared with sequences from baseline samples to detect resistance-associated variants that emerged during treatment. Resistance-associated variants that were present in >1% of sequence reads were reported.		

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
	• ALT normalisation • HRQL (SF-36, CLDQ-HCV, FACIT-F and WPAI)		

AE, adverse event; CHC, chronic hepatitis C; CLDQ, Chronic Liver Disease Questionnaire; CPT, Child-Pugh-Turcotte; ECG, electrocardiogram; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; FACIT-F, Fatigue Index; FAS, full analysis set; GCSF, granulocyte colony stimulating factor; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQL, Health Related Quality of Life; INR, International Normalised Ratio; IWRS, interactive web response system; LLOQ, lower limit of quantitation; MELD, Model for End-Stage Liver Disease; RBV, ribavirin; RNA, ribonucleic acid; SF-36, 36-Item Short-Form Survey; SOF, sofosbuvir; SVR, sustained virologic response; TPO, thrombopoietin; VEL, velpatasvir; WPAI, Work Productivity and Activity Impairment.
† Vital signs include resting blood pressure, pulse, respiratory rate and temperature.

4.3.2 *Eligibility criteria*

Summary details of the eligibility criteria for the ASTRAL RCTs are presented in Table 13 and full details are presented in Table 14. The key differences across the trials relate to HCV genotypes. All three trials allowed for inclusion of patients who were HCV treatment-naïve or treatment-experienced. Approximately 20% of patients with compensated cirrhosis were allowed to be enrolled.

Table 13: Summary eligibility criteria

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
HCV genotype	GT3	GT2	GT1, GT2, GT4, GT5, GT6 or indeterminate
Treatment experience	HCV treatment-naïve or treatment-experienced.		
Cirrhosis permitted	Approximately 20%.		
General inclusion criteria	Aged ≥18 years; HCV RNA≥10^4 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); prior exposure to SOF, NS5B or NS5A inhibitors; 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; clinically significant haemoglobinopathy. Contraindication to RBV ***(ASTRAL-2 and ASTRAL-3 only)***.		

CHC, chronic hepatitis C; CV, cardiovascular; ECG, electrocardiogram; GI, gastrointestinal; GT, genotype; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN interferon; RBV, ribavirin; RNA, ribonucleic acid.

Table 14: Detailed eligibility criteria

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
Inclusion criteria			
HCV genotype	GT3 at screening. Non-definitive results led to study exclusion.	GT2 at screening. Non-definitive results led to study exclusion.	GT1, GT2, GT4, GT5, GT6 or indeterminate
Treatment experience	***HCV treatment-naïve*** • No prior exposure to any IFN, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent ***HCV treatment-experienced*** • Prior treatment failure to a regimen containing IFN+/-RBV completed ≥8 weeks prior to baseline. Patients must not have discontinued prior therapy that resulted in virologic failure due to an AE. The patient's medical records must have included sufficient detail of prior virologic failure to allow categorisation of prior response, as either: ○ Non-responder: patient did not achieve undetectable HCV RNA levels (HCV RNA≥LLOQ) while on treatment, or ○ Relapse/breakthrough: patients achieved undetectable HCV RNA levels (HCV RNA<LLOQ) during treatment or within 4 weeks of the end of treatment but did not achieve SVR		
Cirrhosis permitted	***Presence of cirrhosis in approximately 20% of patients*** • 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 ○ Fibroscan with a result >12.5 kPa • Absence of cirrhosis was defined as any one of the following: ○ Liver biopsy within 2 years of screening showing absence of cirrhosis ○ FibroTest® score of ≤0.48 and APRI of ≤1 during screening ○ Fibroscan with a result of ≤12.5 kPa within 6 months of baseline • In the absence of a definitive diagnosis of presence or absence of cirrhosis by Fibrotest®/APRI using the above criteria, a liver biopsy or fibroscan was required. Liver biopsy results superseded any Fibrotest®/APRI or fibroscan results and were considered definitive • Liver imaging within 6 months of baseline visit was required in cirrhotic patients to exclude HCC		
General inclusion criteria	• Willing and able to provide written informed consent • Aged ≥18 years • HCV RNA≥10^4 IU/mL at screening		

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
	• Chronic HCV infection (≥6 months) determined by prior medical history or liver biopsy • Females of childbearing potential must have had a negative serum pregnancy test at screening and a negative urine pregnancy test on baseline prior to randomisation • 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 protocol; patients under evaluation for a potentially clinically significant illness (other than HCV) were also excluded ○ Gastrointestinal 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 ○ Clinical hepatic decompensation ○ Solid organ transplantation ○ Significant pulmonary disease, significant cardiac disease, or porphyria ○ Psychiatric hospitalisation, suicide attempt, and/or a period of disability as a result of psychiatric illness within the last 5 years. Patients with psychiatric illness (other than the prior mentioned conditions) that was well-controlled on a stable treatment regimen for ≥12 months prior to randomisation or had not required medication in the last 12 months could be included ○ 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) • ECG at screening with clinically significant abnormalities • Laboratory parameters at screening: ○ ALT >10 x ULN ○ AST >10 x ULN ○ Direct bilirubin >1.5 x ULN		

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
	○ Platelets <50,000/µl ○ HbA_{1c} >8.5% ○ CL_{cr} <60 mL/min ○ Haemoglobin <11 g/dL for female patients; <12 g/dL for male patients ○ Albumin <3 g/dL ○ INR >1.5 x ULN unless patient had known haemophilia or was stable on an anticoagulant regimen affecting INR • Prior exposure to SOF or other nucleotide analogue HCV NS5B inhibitor or any HCV NS5A inhibitor • Pregnant or nursing female or male with pregnant female partner • 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 12 • Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent >10 mg/day) • Known hypersensitivity to VEL, SOF, or formulation recipients ○ ASTRAL-2 and ASTRAL-3 only: in addition hypersensitivity to RBV • History of clinically significant haemoglobinopathy (e.g. sickle cell disease, thalassemia)		
Trial specific exclusion criteria	• Contraindication to RBV therapy ***(ASTRAL-2 and ASTRAL-3 only)***		

ALT, alanine aminotransferase; APRI, ratio index; AST, aspartate aminotransferase; CHC, chronic hepatitis C; CL_{cr}, creatinine clearance; CT, computed tomography; ECG, electrocardiogram; EOT, end of treatment; GM-CSF, granulocyte-macrophage colony-stimulating factor; $bHbA_{1c}$, haemoglobin A_{1c}; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus, IFN, interferon; INR, International Normalised Ratio of prothrombin time; MRI, magnetic resonance imaging; NS5A, non-structural protein 5A; NS5B, non-structural protein 5B; OPTN, Organ Procurement and Transplantation Network; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; ULN, upper limit of the normal range; VEL, velpatasvir.

4.3.3 *Study outcomes*

The same primary and secondary outcomes were investigated in the ASTRAL RCTs, and are listed in Table 12. The relevance of each outcome to the decision problem and their validity in current practice are presented in Table 15. ASTRAL-4, described in Section 4.10.9.1, also used the same primary and secondary outcomes, as well as measures of liver function (Model for End-Stage Liver Disease [MELD] and Child-Pugh-Turcotte [CPT] scores).

Table 15: Outcomes investigated in the ASTRAL 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 (14).
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 sofosbuvir-based regimens.
HCV RNA change from baseline		
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). For patients receiving a Peg-IFN+RBV regimen the mechanism of treatment failure (non-response vs relapse) is a good predictor of future response to a Peg-IFN-based regimen.
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.

Outcomes and measures	Included in NICE scope	Reliability/validity/current use in clinical practice
Other outcomes of interest		
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; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FAS, full analysis set; 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; Peg-IFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SF-36, Short Form Health Survey; SVR, sustained virologic response; WPAI: Hep C, Work Productivity and Activity Impairment: Hepatitis C.
† LLOQ=15 IU/mL.

4.4 *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

Analysis sets

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

FAS: Patients who were randomised into the study and received at least one dose of study drug. Patients were grouped by the treatment group to which they were randomised. 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 one 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.

Table 16: Summary of statistical analyses

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
Hypothesis objective	The primary efficacy hypothesis was that the rate of SVR among patients receiving SOF/VEL would be non-inferior to that among patients receiving SOF+RBV.	The primary efficacy hypothesis was that the rate of SVR among patients receiving SOF/VEL would be non-inferior to that among patients receiving SOF+RBV.	• The primary efficacy hypothesis was that the rate of SVR among patients receiving SOF/VEL would be superior to the pre-specified SVR of 85% • This 85% rate was not a historical control derived from rates of SVR in prior HCV treatment trials, since it would not be possible to calculate a single historical rate for the different standard treatments recommended for the various genotypes included in this study. Rather, it is a benchmark rate that is based on the general trend toward increasing rates of SVR in recent years and the general appeal of using a fixed, clinically relevant threshold as a measure of treatment benefit (78)
Statistical analysis of primary endpoint	• A non-inferiority margin of 10 percentage points was applied. If the lower boundary of the 95% CI for the strata-adjusted between-group difference in proportions was more than –10%, a two-sided stratified Cochran‑Mantel‑Haenszel test would be used to test for the superiority of SOF/VEL over SOF+RBV at a significance level of 0.05 • Point estimates and two-sided 95% exact CIs based on the Clopper–Pearson method are provided for SVR rates for all treatment groups		• Point estimates and two-sided 95% exact CIs based on the Clopper–Pearson method are provided for SVR rates for the SOF/VEL group, as well as according to HCV genotype (1a, 1b, 2, 4, 5, or 6)
Statistical analysis of secondary efficacy endpoints	• Proportion of patients with SVR4 and SVR24: SVR4 and SVR24 results were summarised. • 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 proportion of patients with HCV RNA <LLOQ at each visit by treatment group. 'HCV RNA <LLOQ' was split into two categories: <LLOQ TND (for patients with target not detected) and <LLOQ detected (for patients with <LLOQ) ○ In ASTRAL-1 the SOF/VEL group was further broken down by HCV genotype (GT1 [GT1a, GT1b], GT2, GT4, GT5, GT6) • 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 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		

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
	performed ○ In ASTRAL-1 the SOF/VEL group was further broken down by HCV genotype (GT1 [GT1a, GT1b], GT2, GT4, GT5, GT6) • Virologic failure: Descriptively summarised as 'on-treatment virologic failure' and 'relapse'. 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 patients in the FAS. Virologic outcomes were also provided by cirrhosis status and prior treatment experience ○ In ASTRAL-1 the SOF/VEL group was further broken down by HCV genotype (GT1 [GT1a, GT1b], GT2, GT4, GT5, GT6) • 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 • ALT normalisation: similar methodology to the analyses of HCV RNA<LLOQ, using a missing=excluded analysis. Only patients with ALT >ULN range at baseline were to be included in the analysis • 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 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		
Sample size, power calculation	A sample size of 250 patients in each treatment group was calculated to provide a power of 94% to establish non-inferiority between the two groups, on the basis of an SVR rate of 89%, using a one-sided test at significant level of 0.025.	A sample size of 120 patients in each treatment group was calculated to provide a power of 90% to establish non-inferiority between the two groups, on the basis of an SVR rate of 94%, using a one-sided test at significant level of 0.025.	A sample size of 500 patients in the SOF/VEL group was calculated to provide a power of 90% to detect an improvement of ≥5 percentage points in the rate of SVR over the pre-defined performance goal of 85%, on the basis of the two-sided exact one-sample binomial test at the 0.05 significance level.
Data management, patient withdrawals	• 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) • Patients with missing data due to premature discontinuation of the study had missing data imputed up to the time of their last dose (if last dose was on-treatment). If study day associated with the last dose was ≥the lower bound of a visit window, and the value at visit was missing, then the value was imputed. If the study day associated with the last dose was <the lower bound of the visit window, then		

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
	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 1 IU/mL. No other imputations were performed for continuous data • For HRQL data, missing data at on-treatment visits and 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		

CHC, chronic hepatitis C; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CSR, clinical study report; 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; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected; VEL, velpatasvir.

4.5 *Participant flow in the relevant randomised controlled trials*

4.5.1 *Patient disposition*

CONSORT flow charts for all ASTRAL RCTs are presented in Figure 3, Figure 4, and Figure 5. The primary analyses in all trials were based on the FAS.

- In ASTRAL-3, 652 patients were initially screened. Of these, 558 patients were randomised and 552 received at least one dose of the study drug (FAS); 277 in the SOF/VEL group and 275 in the SOF+RBV group.
- In ASTRAL-2, 317 patients were initially screened. Of these, 269 patients were randomised and 266 received at least one dose of the study drug (FAS); 134 in the SOF/VEL group and 132 in the SOF+RBV group.
- In ASTRAL-1, 847 patients were initially screened. Of these, 706 patients were randomised and a further 35 with CHC GT5 were assigned directly to SOF/VEL. Overall 740 patients received at least one dose of study drug (FAS); 624 in the SOF/VEL group and 116 in the placebo group.

Reasons for premature discontinuation of study treatment are provided in Table 17, Table 18 and Table 19.

4.5.1.1 ASTRAL-3

Figure 3: Patient disposition in ASTRAL-3

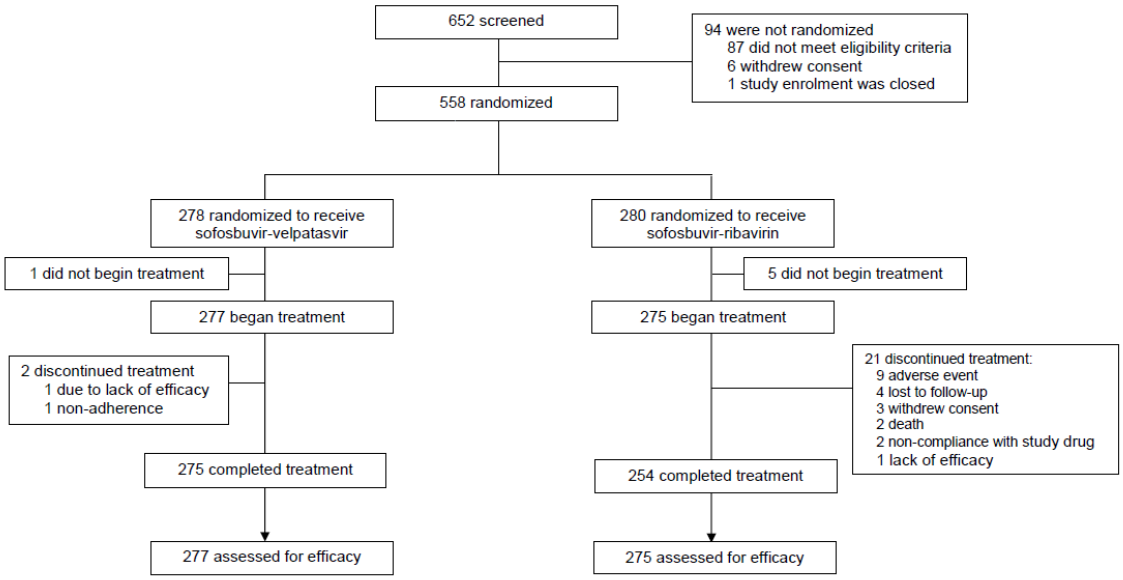


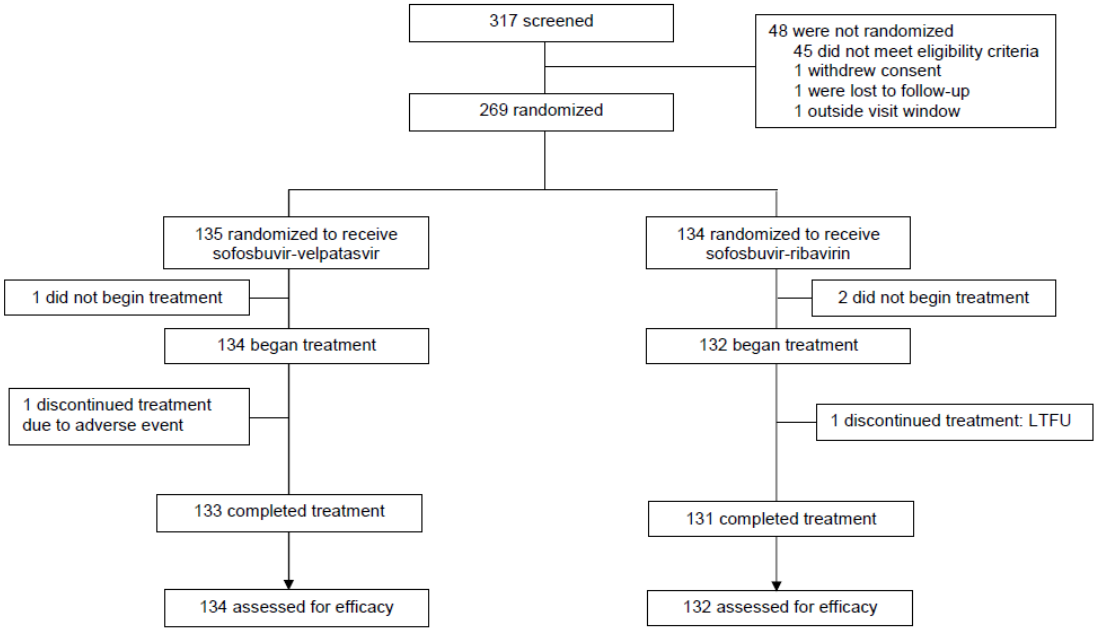
Table 17: Reasons for premature discontinuation of study treatment in ASTRAL-3 (FAS)

	SOF/VEL N=277	SOF+RBV N=275	Total N=552
Total premature discontinuations, n (%)	2 (0.7)	21 (7.6)	23 (4.2)
Adverse event, n (%)	0	9 (3.3)	9 (1.6)
Lost to follow-up, n (%)	0	4 (1.5)	4 (0.7)
Non-compliance with study drug, n (%)	1 (0.4)	2 (0.7)	3 (0.5)
Withdrew consent, n (%)	0	3 (1.1)	3 (0.5)
Death, n (%)	0	2 (0.7)	2 (0.4)
Lack of efficacy, n (%)	1 (0.4)	1 (0.4)	2 (0.4)

RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

4.5.1.2 ASTRAL-2

Figure 4: Patient disposition in ASTRAL-2



LTFU, lost to follow up.

Table 18: Reasons for premature discontinuation of study treatment in ASTRAL-2 (FAS)

	SOF/VEL N=134	SOF+RBV N=132	Total N=266
Total premature discontinuations, n (%)	1 (0.7)	1 (0.8)	2 (0.8)
Adverse event, n (%)	1 (0.7)	0	1 (0.4)
Lost to follow-up, n (%)	0	1 (0.8)	1 (0.4)

RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

4.5.1.3 *ASTRAL-1*

Figure 5: Patient disposition in ASTRAL-1

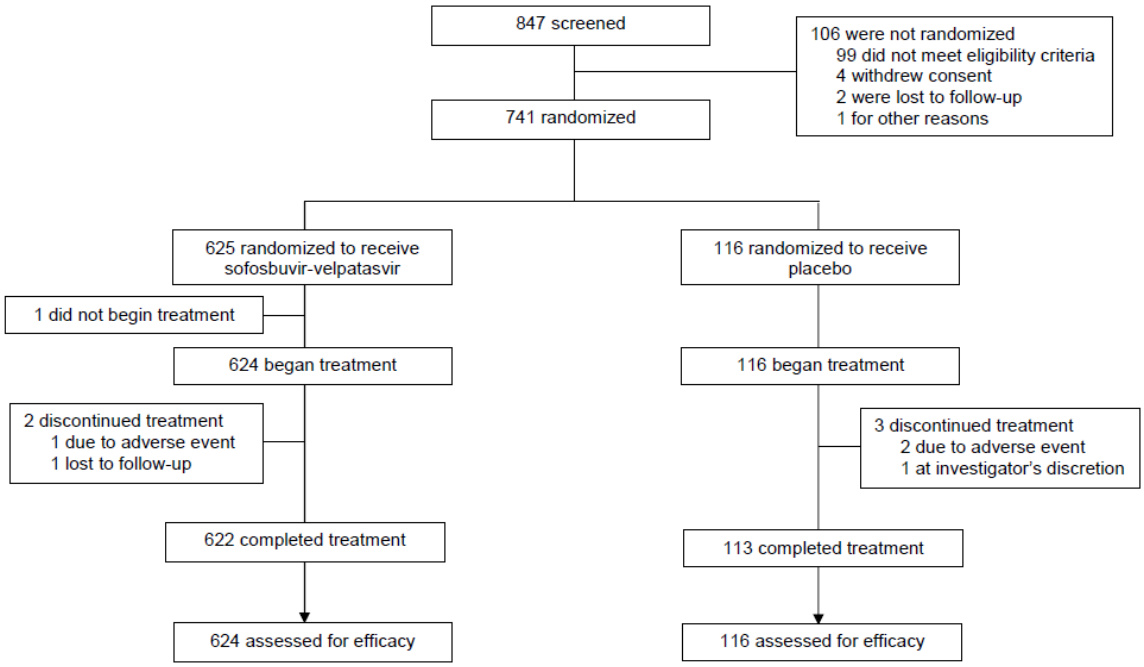


Table 19: Reasons for premature discontinuation of study treatment in ASTRAL-1 (FAS)

	SOF/VEL N=624	Placebo N=116	Total N=740
Total premature discontinuations, n (%)	2 (0.3)	3 (2.6)	5 (0.7)
Adverse event, n (%)	1 (0.2)	2 (1.7)	3 (0.4)
Lost to follow-up, n (%)	1 (0.2)	0	1 (0.1)
Investigator's discretion, n (%)	0	1 (0.9)	1 (0.1)

SOF, sofosbuvir; VEL, velpatasvir.

4.5.2 *Baseline characteristics and demographics*

4.5.2.1 *ASTRAL-3*

In ASTRAL-3, demographics and baseline characteristics were generally balanced across both treatment groups (Table 20). Overall, the majority of patients were male (62%) and white (89%), with a mean age of 50 years (range: 19–76). The majority of patients were from countries outside the US (78.3%). Baseline disease characteristics were also generally balanced across both treatment groups. All patients had GT3 CHC infection. The majority of patients had non-CC IL28B alleles (61%), 29.5% had cirrhosis at screening and 26% were treatment-experienced; [redacted] and had failed previous treatment as a result of breakthrough or relapse (69%).

Table 20: Characteristics of participants in ASTRAL-3 (FAS)

Characteristic	SOF/VEL N=277	SOF+RBV N=275

Characteristic	SOF/VEL N=277	SOF+RBV N=275
Mean age (range), years	49 (21–76)	50 (19–74)
Male, n (%)	170 (61)	174 (63)
Mean BMI (range), kg/m2†	26 (17–48)	27 (17–56)
Race, n (%)‡		
White	250 (90)	239 (87)
Black	3 (1)	1 (<1)
Asian	23 (8)	29 (11)
Other	1 (<1)	6 (2)
Mean HCV RNA±SD, log10 IU/mL	6.2±0.72	6.3±0.71
HCV RNA≥800,000 IU/mL, n (%)	191 (69)	194 (71)
IL28B genotype, n (%)		
CC	105 (38)	111 (40)
CT	148 (53)	133 (48)
TT	24 (9)	31 (11)
Compensated cirrhosis, n (%)	80 (29)	83 (30)
Previous HCV treatment, n (%)		
No	206 (74)	204 (74)
Yes	71 (26)	71 (26)
Type of previous HCV treatment, n/total (%)		
DAA+Peg-IFN+RBV	[redacted]	[redacted]
Peg-IFN+RBV	[redacted]	[redacted]
Other	[redacted]	[redacted]
Response to previous HCV treatment, n/total (%)		
No response	20/71 (28)	24/71 (34)
Relapse/breakthrough	51/71 (72)	47/71 (66)

BMI, body mass index; DAA, direct acting antiviral; HCV, hepatitis C virus; Peg-IFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; VEL, velpatasvir
† BMI is the weight in kg divided by the height squared in metres; ‡ race was self-reported.

4.5.2.2 ASTRAL-2

In ASTRAL-2, demographics and baseline characteristics were generally balanced across both treatment groups (Table 21). Overall, the majority of patients were male (59%) and white (88%), with a mean age of 57 years (range: 23–81). Baseline disease characteristics were also generally balanced across both treatment groups. All patients had GT2 CHC infection. The majority of patients had non-CC IL28B alleles (62%), 14% had cirrhosis at screening and 15% were treatment-experienced; [redacted] and had failed previous treatment as a result of breakthrough or relapse (85%).

Table 21: Characteristics of participants in ASTRAL-2 (FAS)

Characteristic	SOF/VEL N=134	SOF+RBV N=132
Mean age (range), years	57 (26–81)	57 (23–76)
Male, n (%)	86 (64)	72 (55)
Mean BMI (range), kg/m2†	28 (17–45)	29 (19–61)
Race, n (%)‡		
White	124 (93)	111 (84)
Black	6 (4)	12 (9)
Asian	1 (1)	5 (4)
Other	3 (2)	4 (3)
Mean HCV RNA±SD, log10 IU/mL	6.5±0.78	6.4±0.74
HCV RNA≥800,000 IU/mL, n (%)	111 (83)	101 (77)
IL28B genotype, n (%)		
CC	55 (41)	46 (35)
CT	61 (46)	64 (48)
TT	18 (13)	22 (17)
Compensated cirrhosis, n (%)	19 (14)	19 (14)
Previous HCV treatment, n (%)		
No	115 (86)	112 (85)
Yes	19 (14)	20 (15)
Type of previous HCV treatment, n/total (%)		
Peg-IFN+RBV	[redacted]	[redacted]
Other	[redacted]	[redacted]
Response to previous HCV treatment, n/total (%)		
No response	3/19 (16)	3/20 (15)
Relapse/breakthrough	16/19 (84)	17/20 (85)

BMI, body mass index; DAA, direct acting antiviral; HCV; hepatitis C virus; Peg-IFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; VEL, velpatasvir
† BMI is the weight in kg divided by the height squared in metres; ‡ race was self-reported.

4.5.2.3 ASTRAL-1

In ASTRAL-1, demographics and baseline characteristics were generally balanced across both treatment groups (Table 22). Overall, the majority of patients were male (60%) and white (79%), with a mean age of 54 years (range: 18–82). Baseline disease characteristics were also generally balanced across both treatment groups. In the SOF/VEL group 34% of patients had CHC GT1a, 19% GT1b, 17% GT2, 19% GT4, 6% GT5, and 7% GT6. The majority of patients had non-CC IL28B alleles (69%), 19% had cirrhosis at screening and 32% were HCV treatment-experienced.

Of those in the SOF/VEL group who had received previous treatment (n=201), 28% had received a regimen of PI+Peg-IFN+RBV, and 61% had received Peg-IFN+RBV; 48% of these

patients had persistently detectable HCV RNA while receiving previous treatment (no response), and 51% had a virologic relapse or breakthrough. A total of 51% of patients were enrolled in Europe, 46% in North America (Canada and the United States), and 3% in Hong Kong.

Table 22: Characteristics of participants in ASTRAL-1 (FAS)

Characteristic	SOF/VEL N=624	Placebo N=116
Mean age (range), years	54 (18–82)	53 (25–74)
Male, n (%)	374 (60)	68 (59)
Mean BMI (range), kg/m2[†]	27 (17–57)	26 (18–40)
Race, n (%)[‡]		
White	493 (79)	90 (78)
Black	52 (8)	11 (9)
Asian	62 (10)	11 (9)
Other	14 (2)	4 (3)
HCV genotype		
1a	210 (34)	46 (40)
1b	118 (19)	19 (16)
2	104 (17)	21 (18)
4	116 (19)	22 (19)
5[§]	35 (6)	0
6	41 (7)	8 (7)
Mean HCV RNA±SD, log10 IU/mL	6.3±0.66	6.3±0.58
HCV RNA≥800,000 IU/mL, n (%)	461 (74)	87 (75)
IL28B genotype, n (%)		
CC	186 (30)	36 (31)
CT	339 (54)	53 (46)
TT	94 (15)	26 (22)
Missing data	5 (1)	1 (1)
Compensated cirrhosis, n (%)	121 (19)	21 (18)
Previous HCV treatment, n (%)		
No	423/624 (68)	83/116 (72)
Yes	201/624 (32)	33/116 (28)
Type of previous HCV treatment, n/total (%)		
DAA+Peg-IFN+RBV	56/201 (28)	6/33 (18)
Peg-IFN+RBV	122/201 (61)	24/33 (73)
Non Peg-IFN+/-RBV	23/201 (11)	3/33 (9)
Response to previous HCV treatment, n/total (%)		
No response	[redacted] (48)	[redacted]

Characteristic	SOF/VEL N=624	Placebo N=116
Relapse/breakthrough	[redacted] (51)	[redacted]

BMI, body mass index; DAA, direct acting antiviral; HCV, hepatitis C virus; Peg-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; VEL, velpatasvir
† BMI is the weight in kg divided by the height squared in metres; ‡ race was self-reported; § Patients with HCV GT5 infection did not undergo randomisation but were enrolled in the SOF/VEL group.

4.6 *Quality assessment of the relevant randomised controlled trials*

Table 23: Quality assessment results for parallel group RCTs

	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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

GT, genotype; CHC, chronic hepatitis C.

A complete quality assessment for each RCT is provided in Appendix 4.

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

4.7.1 *ASTRAL-3*

Primary and secondary efficacy results for ASTRAL-3 are presented in Table 24.

4.7.1.1 Primary efficacy results: SVR12

Among patients with GT3 HCV infection the SVR rate 12 weeks after treatment with SOF/VEL for 12 weeks was 95.3% [redacted] compared with 80.7% [redacted] in patients who received 24 weeks of treatment with SOF+RBV.

The primary efficacy endpoint was met. The SVR12 rate for the SOF/VEL 12 week group was statistically non-inferior to the SVR12 rate for the SOF+RBV 24 week group; strata-adjusted difference [redacted] with the lower bound of the two-sided 95% CI for the difference being greater than the pre-specified non-inferiority margin of −10%.

SOF/VEL 12 weeks was also shown to be superior to SOF+RBV for 24 weeks (p<0.001; Cochran-Mantel-Haenszel [CMH] test stratified by cirrhosis status and prior treatment experience).

Table 24: Summary of response during and after treatment in ASTRAL-3 (FAS)

Response	SOF/VEL 12 weeks N=277	SOF+RBV 24 weeks N=275
HCV RNA<LLOQ		
During treatment, n/N (%)[†]		
At week 2	171/276 (62.0)	137/274 (50.0)
95% CI	[redacted]	[redacted]
At week 4	253/276 (91.7)	240/272 (88.2)
95% CI	[redacted]	[redacted]
At week 6	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
At week 8	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Post-treatment, n/N (%)		
At week 4 (SVR4)	268/277 (96.8)	226/275 (82.2)
95% CI	[redacted]	[redacted]
At week 12 (SVR12)	264/277 (95.3)	222/275 (80.7)
95% CI	[redacted]	[redacted]
p-value	<0.001	-
Difference, % (95% CI)	[redacted]	-
Outcome for patients without SVR12, n/N (%)		
Total	13/277 (4.7)	53/275 (19.3)
Overall virologic failure	11/277 (4.0)	39/275 (14.2)

Response	SOF/VEL 12 weeks N=277	SOF+RBV 24 weeks N=275
Relapse[§]	11/276 (4.0)	38/272 (14.0)
On-treatment failure[§]	0/277 (0)	1/275 (0.4)
Other[‡]	2/277 (0.7)	14/275 (5.1)

CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.
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; ‡ patients who did not achieve SVR12 and did not meet virologic failure criteria; § Denominator for relapse is the number of patients who had HCV RNA <LLOQ on their last observed on-treatment HCV RNA measurement.

4.7.1.2 Secondary efficacy outcomes

Proportion of patients with SVR at 4 and 24 weeks

Overall, the SVR4 results were similar to the SVR12 results; SVR4 rates were 96.8% in the SOF/VEL group and 82.2% in the SOF+RBV group.

[redacted]

Proportion of patients with HCV RNA <LLOQ on treatment

A summary of the proportion of patients with HCV RNA <LLOQ on treatment at weeks 2, 4, 6, and 8 is presented in Table 24. There was a potent and rapid suppression of HCV RNA while on treatment observed in both treatment groups. As early as week 4, ≥88% of patients in both treatment groups had achieved HCV RNA <LLOQ.

HCV change from baseline

HCV RNA levels declined rapidly, with similar decreases in HCV RNA observed in both treatment groups. After 1 week of treatment, the mean (SD) change from baseline in HCV RNA levels was [redacted] $\log_{10}$ IU/mL in the SOF/VEL 12 week group and [redacted] IU/mL in the SOF+RBV 24 week group. The decreases in HCV RNA levels [redacted] from week 2 through end of treatment (EOT), with mean changes from baseline ranging from [redacted] $\log_{10}$ IU/mL across both treatment groups.

Proportion of patients with virologic failure

Among the 277 patients who received SOF/VEL, 11 (4.0%) relapsed after the end of treatment, and two patients were lost to follow-up (Table 24).

Among the 275 patients who received SOF+RBV, 38 (14.0%) had a relapse after treatment and one had virologic failure on-treatment. Of the remaining 14 patients, five were lost to follow-up, four discontinued treatment because of AEs, two withdrew consent, two died, and one discontinued treatment before achieving undetectable HCV RNA.

Development of resistance

Of 274 patients in the SOF/VEL group who had available data on virologic outcome (SVR or virologic failure) with deep sequencing data, 43 (15.7%) had detectable NS5A resistance-

associated variants (A30K, L31M, and Y93H) at baseline. Of these patients, 38 (88.4%) had an SVR. Of the 25 patients with the Y93H variant at baseline, 21 (84.0%) had an SVR. Of those patients who relapsed, five patients had detectable NS5A resistance-associated variants at baseline and ten patients had mutations at the time of relapse. One additional patient who was classified as relapsed experienced reinfection with HCV GT1a.

Of the 231 patients without NS5A resistance-associated variants at baseline, 225 (97.4%) had an SVR.

All 10 patients with baseline NS5B resistance-associated variants (N142T, L159F, E237G, L320I, and V321A/I) had an SVR.

4.7.1.3 Other outcomes of interest

ALT normalisation

Coincident with decreases in HCV RNA, [redacted] Median changes from baseline ranged from [redacted] across 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 whether they had achieved SVR or not. These HRQL results should be interpreted with caution as multiple endpoints were tested and the study was not powered to test these exploratory endpoints.

Overall, results from the HRQL questionnaires indicated that no on-treatment decrements in HRQL were observed in the SOF/VEL 12 week group. However, in the SOF+RBV 24 week group, statistically significant ($p<0.05$) worsening in HRQL was observed between baseline and EOT for the SF-36 (domains of role physical, social functioning, mental health, and mental component) and WPAI: Hep C (percent overall work impairment due to HCV). The mean scores for most scales improved from EOT to post-treatment week 4 and 12 weeks.

Table 25: Summary of HRQL outcomes (ASTRAL-3)

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 12 weeks			SOF+RBV 12 weeks		
SF-36, Physical component	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36, Mental component	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CLDQ-HCV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F Trial Outcome Index	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F Total score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI, percentage of overall work impairment due to HepC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI, percentage of activity impairment due to HepC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BL, baseline; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; EOT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HepC, hepatitis C; HRQL, health related quality of life; PT, post-treatment; RBV, ribavirin; SD, standard deviation; SF-36, Short Form Health Survey; SOF, sofosbuvir; VEL, velpatasvir; WPAI, Work Productivity and Activity Impairment.
†p-value for change from baseline to time point; ‡p-value for between treatment difference for change from baseline.
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 (ASTRAL-3)

- SOF/VEL administered as an STR once daily for 12 weeks to patients with chronic GT3 HCV infection was superior to SOF+RBV given for 24 weeks, resulting in an SVR12 of 95.3% [redacted]; p<0.001) compared with 80.7% [redacted]
- SVR12 rates with SOF/VEL 12 weeks were consistently high (>89%), irrespective of presence or absence of cirrhosis, or prior treatment experience (see Section 4.8):
  - Treatment-naïve without cirrhosis: 98.2% SOF/VEL versus 91.0% SOF+RBV
  - Treatment-naïve with cirrhosis: 93.0% SOF/VEL versus 73.3% SOF+RBV
  - Treatment-experienced without cirrhosis: 91.2% SOF/VEL versus 71.0% SOF+RBV
  - Treatment-experienced with cirrhosis: 89.2% SOF/VEL versus 57.9% SOF+RBV
- Of 277 patients treated with SOF/VEL, 11 patients experienced virologic failure, all as a result of relapse following completion of treatment. By comparison, 38 of 275 patients treated with SOF+RBV had a relapse and one patient had virologic breakthrough while on treatment
- Of those patients who relapsed following SOF/VEL treatment, five patients had NS5A resistance-associated variants at baseline and 10 had NS5A resistance-associated variants at the time of 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
- There was no evidence of outcomes being affected by mutations conferring resistance to SOF (NS5B resistance-associated variants)
- HRQL was assessed using the SF-36, CLDQ-HCV, FACIT-F and WPAI: Hep C questionnaires. Patients treated with SOF/VEL experienced no decrements in HRQL while on treatment. Mean scores of most scales improved from the end of treatment to post-treatment week 4 and 12

4.7.2 *ASTRAL-2*

Primary and secondary efficacy results for ASTRAL-2 are presented in Table 26.

4.7.2.1 Primary efficacy results: SVR12

Among patients with GT2 HCV infection the SVR rate 12 weeks after treatment with SOF/VEL for 12 weeks was 99.3% [redacted] compared with 93.9% [redacted] in patients who received 12 weeks of treatment with SOF+RBV.

The primary efficacy endpoint was met. The SVR12 rate for the SOF/VEL 12 week group was statistically non-inferior to the SVR12 rate for the SOF+RBV 12 week group; strata-adjusted difference 5.2% (95% CI: 0.2, 10.3) with the lower bound of the two-sided 95% CI for the difference being greater than the pre-specified non-inferiority margin of −10%.

SOF/VEL 12 weeks was also shown to be superior to SOF+RBV for 12 weeks (p=0.018; CMH test stratified by cirrhosis status and prior treatment experience).

Table 26: Summary of response during and after treatment in ASTRAL-2 (FAS)

Response	SOF/VEL 12 weeks N=134	SOF+RBV 12 weeks N=132
HCV RNA<LLOQ		
During treatment, n/N (%)[†]		
At week 2	76/133 (57.1)	79/132 (59.8)
95% CI	[redacted]	[redacted]
At week 4	120/133 (90.2)	119/132 (90.2)
95% CI	[redacted]	[redacted]
At week 6	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
At week 8	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Post-treatment, n/N (%)		
At week 4 (SVR4)	133/134 (99.3)	127/132 (96.2)
95% CI	[redacted]	[redacted]
At week 12 (SVR12)	133/134 (99.3)	124/132 (93.9)
95% CI	[redacted]	[redacted]
p-value	[redacted]	-
Difference, % (95% CI)	5.2 (0.2, 10.3)	-
Outcome for patients without SVR12, n/N (%)		
Total	1/134 (0.7)	8/132 (6.1)
Overall virologic failure	0/134	6/132 (4.5)
Relapse[§]	0/133	6/132 (4.5)

Response	SOF/VEL 12 weeks N=134	SOF+RBV 12 weeks N=132
On-treatment failure	0/134	0/132
Other‡	1/134 (0.7)	2/132 (1.5)

CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.
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; ‡ patients who did not achieve SVR12 and did not meet virologic failure criteria; § Denominator for relapse is the number of patients who had HCV RNA <LLOQ on their last observed on-treatment HCV RNA measurement.

4.7.2.2 Secondary efficacy outcomes

Proportion of patients with SVR at 4 and 24 weeks

Overall, the SVR4 results were similar to the SVR12 results; SVR4 rates were 99.3% in the SOF/VEL group and 96.2% in the SOF+RBV group.

[redacted]

Proportion of patients with HCV RNA <LLOQ on treatment

A summary of the proportion of patients with HCV RNA <LLOQ on treatment at weeks 2, 4, 6, and 8 is presented in Table 26. There was a potent and rapid suppression of HCV RNA while on treatment observed in both treatment groups. As early as week 4, ≥90% of patients in both treatment groups had achieved HCV RNA <LLOQ.

HCV change from baseline

HCV RNA levels declined rapidly, with similar decreases in HCV RNA observed in both treatment groups. After 1 week of treatment, the mean (SD) change from baseline in HCV RNA levels was [redacted] $\log_{10}$ IU/mL in the SOF/VEL 12 week group and [redacted] IU/mL in the SOF+RBV 12 week group. The decreases in HCV RNA levels [redacted] from weeks 2 through EOT, with mean changes from baseline ranging from [redacted] IU/mL across both treatment groups.

Proportion of patients with virologic failure

Among the 134 patients who received SOF/VEL for 12 weeks, there were no virologic failures either on-treatment or after the end of treatment. One patient discontinued on day 1 after receiving one dose of study drug due to AEs (Table 26).

Among the 132 patients who received SOF+RBV for 12 weeks, six (4.5%) had a relapse after the end of treatment, and none had virologic failure on-treatment. Two patients were lost to follow-up.

Development of resistance

Deep sequencing data indicated that approximately 60% of the 134 patients in the SOF/VEL group had NS5A resistance-associated variants and 10% had NS5B resistance-associated variants at baseline. The most prevalent NS5A variant observed at baseline was L31M in 52%

of patients. Despite the presence of pre-treatment NS5A and NS5B resistance-associated variants in the ASTRAL-2 trial, no patient receiving SOF/VEL had virologic failure.

4.7.2.3 Other outcomes of interest

ALT normalisation

Coincident with decreases in HCV RNA, [redacted] Median changes from baseline ranged from [redacted] across 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 whether they had achieved SVR or not. These HRQL results should be interpreted with caution as multiple endpoints were tested and the study was not powered to test these exploratory endpoints.

Overall, results from all HRQL questionnaires indicated that no on-treatment decrements in HRQL were observed in the SOF/VEL 12 week group.

In the SOF+RBV 12 week group, statistically significant ($p<0.05$) worsening in HRQL was observed between baseline and EOT for the SF-36 domain of role emotional and a statistically significant improvement was observed for bodily pain. In addition, in the SOF+RBV 12 week group, numeric worsening from baseline to EOT was observed in 5 of 8 domain scores of the SF-36 (domains of role physical, vitality, social functioning, role emotional, and mental health), and the mental component score. Numeric improvement from baseline in the SOF+RBV 12 week group was observed for the SF-36 domains of physical functioning, bodily pain, general health, and the physical component score.

The mean scores for most scales improved from EOT to post-treatment week 4 and 12 weeks.

Table 27: Summary of HRQL outcomes (ASTRAL-2)

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 12 weeks			SOF+RBV 12 weeks		
SF-36, Physical component	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36, Mental component	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CLDQ-HCV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F Trial Outcome Index	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F Total score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI, percentage of overall work impairment due to HepC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI, percentage of activity impairment due to HepC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

†p-value for change from baseline to time point; ‡p-value for between treatment difference for change from baseline.

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 (ASTRAL-2)

- SOF/VEL administered as an STR once daily for 12 weeks to patients with chronic GT2 HCV infection was superior to SOF+RBV given for 12 weeks, resulting in an SVR12 of 99.3% [redacted] compared with 93.9% [redacted]
- SVR12 rates with SOF/VEL 12 weeks were consistently high (≥99%), irrespective of presence or absence of cirrhosis, or prior treatment experience (see Section 4.8)
- Of 134 patients treated with SOF/VEL, no patients experienced virologic failure. One patient did not achieve SVR12 as a result of treatment discontinuation on day 1 of treatment. By comparison, six of 132 patients treated with SOF+RBV had a relapse and two were lost to follow up
- The presence of baseline NS5A and NS5B resistance-associated variants was not associated with virologic failure
- HRQL was assessed using the SF-36, CLDQ-HCV, FACIT-F and WPAI: Hep C questionnaires. Patients treated with SOF/VEL experienced no decrements in HRQL while on treatment. Mean scores of most scales improved from the end of treatment to post-treatment week 4 and 12

4.7.3 *ASTRAL-1*

Primary and secondary efficacy results for ASTRAL-1 are presented in Table 28.

4.7.3.1 Primary efficacy results: SVR12

Among patients in the overall trial population (with GT1, GT2, GT4, GT5 or GT6 HCV infection) the SVR rate 12 weeks after treatment with SOF/VEL for 12 weeks was 99.0% [redacted]). This was statistically significantly superior to the pre-defined performance goal of 85% (p<0.001). None of the 116 patients in the placebo group achieved an SVR.

SVR12 by genotype

SVR12 rates were similar regardless of the HCV genotype (Table 29):

- GT1a: 98.1% (95% CI: [redacted]
- GT1b: 99.2% (95% CI: [redacted]
- GT2: 100.0% (95% CI: [redacted]
- GT4: 100.0% (95% CI: [redacted]
- GT5: 97.1% (95% CI: [redacted]
- GT6: 100.0% (95% CI: [redacted]

Table 28: Summary of response during and after treatment in ASTRAL-1 (FAS)

Response	**SOF/VEL 12 weeks N=624**
HCV RNA<LLOQ	
During treatment, n/N (%)[†]	
At week 2	355/624 (56.9)
95% CI	[redacted]
At week 4	564/623 (90.5)
95% CI	[redacted]
At week 6	[redacted]
95% CI	[redacted]
At week 8	[redacted]
95% CI	[redacted]
Post-treatment, n/N (%)	
At week 4 (SVR4)	[redacted]
95% CI	[redacted]
At week 12 (SVR12)	618/624 (99.0)
95% CI	[redacted]
p-value[‡]	<0.001
Outcome for patients without SVR12, n/N (%)	
Total	6/624 (1.0)
Overall virologic failure	2/624 (0.3)
Relapse[§]	2/623 (0.3)

Response	SOF/VEL 12 weeks N=624
On-treatment failure	0/624 (0)
Other¶	4/624 (0.6)

CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.
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; ‡ compared with pre-defined performance goal of 85%; § Denominator for relapse is the number of patients who had HCV RNA <LLOQ on their last observed on-treatment HCV RNA measurement; ¶ patients who did not achieve SVR12 and did not meet virologic failure criteria.

Table 29: Summary of SVR12 rates by HCV genotype in ASTRAL-1 (FAS)

Response	SOF/VEL 12 weeks N=624
HCV RNA<LLOQ at week 12 post-treatment (SVR12)	
GT1	
n/N (%)	323/328 (98.5)
95% CI	[redacted]
GT1a	
n/N (%)	206/210 (98.1)
95% CI	[redacted]
GT1b	
n/N (%)	117/118 (99.2)
95% CI	[redacted]
GT2	
n/N (%)	104/104 (100.0)
95% CI	[redacted]
GT4	
n/N (%)	116/116 (100.0)
95% CI	[redacted]
GT5	
n/N (%)	34/35 (97.1)
95% CI	[redacted]
GT6	
n/N (%)	41/41 (100.0)
95% CI	[redacted]

CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.
LLOQ=15 IU/mL.

4.7.3.2 Secondary efficacy outcomes

Proportion of patients with SVR at 4 and 24 weeks

Overall, the SVR4 result was similar to the SVR12 result, with an SVR4 rate of 99.2% in the SOF/VEL group.

[redacted]

Proportion of patients with HCV RNA <LLOQ on treatment

A summary of the proportion of patients with HCV RNA <LLOQ on treatment at weeks 2, 4, 6, and 8 for the overall trial population (all genotypes) is presented in Table 28. There was a potent and rapid suppression of HCV RNA while on treatment with SOF/VEL; as early as week 4, [redacted] of patients in the overall trial population had achieved HCV RNA <LLOQ. [redacted]

HCV change from baseline

HCV RNA levels declined rapidly in the SOF/VEL 12 week group; after 1 week of treatment, the mean (SD) change from baseline in HCV RNA levels was [redacted] log_{10} IU/mL. The decreases in HCV RNA levels [redacted] from weeks 2 through EOT, with mean changes from baseline ranging from [redacted] log_{10} IU/mL across both treatment groups.

[redacted]

Proportion of patients with virologic failure

Among the 624 patients who received SOF/VEL, two (0.3%) experienced virologic failure; both had undetectable serum HCV RNA at week 4 of treatment but suffered relapse by week 4 post-treatment (Table 28). Four additional patients were classified as not having achieved an SVR 12 weeks after the end of treatment: two were lost to follow up; one discontinued treatment due to an AE; one died during follow up.

Development of resistance

At baseline, NS5A resistance-associated variants were detected in 257 of 616 patients (41.7%) for whom sequencing data were available. Of these, 255 (99.2%) had an SVR. The two patients who had virologic failure had NS5A-resistant variants at baseline and at the time of relapse.

Variants associated with resistance to NS5B nucleoside inhibitors were detected at baseline in 54 of 601 patients (9.0%) for whom sequencing data were available. All 54 patients had an SVR.

4.7.3.3 Other outcomes of interest

ALT normalisation

Coincident with decreases in HCV RNA, [redacted]

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 whether they had achieved SVR or not. These HRQL results should be interpreted with caution as multiple endpoints were tested and the study was not powered to test these exploratory endpoints.

Statistically significant ($p<0.05$) improvements in HRQL were generally observed in the SOF/VEL group across all four HRQL tools (Table 30).

During treatment improvements from baseline were generally observed in all 8 domain scores of the SF-36, the mental component score, and the physical component score. Improvements were significant ($p<0.05$) in SF-36 scores for bodily pain general health, vitality, and physical component were observed.

When compared with placebo, significant improvements ($p<0.05$) between baseline and EOT were observed with SOF/VEL for role physical, general heath, vitality, social functioning, and physical component SF-36 scores. Between treatment differences were also significant at 4 and/or 12 weeks post-treatment for role physical, bodily pain, general health, vitality, social function, mental health, the physical component, and the mental component scores.

Between baseline and post-treatment week 12, significant improvements ($p<0.05$) were also observed for the SOF/VEL group versus placebo in CLDQ-HCV (overall score), FACIT-F (trial outcome index and total score), and WPAI (percent activity impairment).

Table 30: Summary of HRQL outcomes (ASTRAL-1)

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 12 weeks			Placebo		
SF-36, Physical component	51.0 (8.88)	[redacted]	[redacted]	51.8 (8.47)	[redacted]	[redacted]
SF-36, Mental component	49.2 (10.39)	[redacted]	[redacted]	51.0 (8.88)	[redacted]	[redacted]
CLDQ-HCV	5.4 (1.09)	[redacted]	[redacted]	5.5 (1.05)	[redacted]	[redacted]
FACIT-F Trial Outcome Index	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F Total score	122.5 (27.52)	[redacted]	[redacted]	126.2 (22.88)	[redacted]	[redacted]
WPAI, percentage of overall work impairment due to HepC	13.5 (22.00)	[redacted]	[redacted]	14.3 (23.53)	[redacted]	[redacted]
WPAI, percentage of activity impairment due to HepC	18.4 (25.99)	[redacted]	[redacted]	13.2 (22.55)	[redacted]	[redacted]

BL, baseline; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; EOT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HepC, hepatitis C; HRQL, health related quality of life; PT, post-treatment; RBV, ribavirin; SD, standard deviation; SF-36, Short Form Health Survey; SOF, sofosbuvir; VEL, velpatasvir; WPAI, Work Productivity and Activity Impairment.
†p-value for change from baseline to time point; ‡p-value for between treatment difference for change from baseline.
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 (ASTRAL-1)

- SOF/VEL administered as an STR once daily for 12 weeks resulted in an SVR 12 weeks after the end of treatment in 99.0% ( ) of patients chronically infected with GT1, GT2, GT4, GT5 or GT6. This was superior to the pre-defined performance goal of 85% ($p<0.001$)
- SVR12 rates were high irrespective of HCV genotype
  - GT1a: 98.1% (95% CI)
  - GT1b: 99.2% (95% CI:)
  - GT2: 100.0% (95% CI:)
  - GT4: 100.0% (95% CI:)
  - GT5: 97.1% (95% CI:)
  - GT6: 100.0% (95% CI:)
- SVR12 rates with SOF/VEL 12 weeks were also consistently high (>98%), irrespective of presence or absence of cirrhosis, or prior treatment experience (see Section 4.8):
- Of 624 patients treated with SOF/VEL, only two (0.3%) patients experienced virologic failure, both as a result of relapse following completion of treatment.
- The presence of baseline NS5A and NS5B resistance-associated variants was not associated with virologic failure
- HRQL was assessed using the SF-36, CLDQ-HCV, FACIT-F and WPAI: Hep C questionnaires. Improvements in HRQL with SOF/VEL were generally observed across all four tools between baseline and post-treatment week 12 which were significantly better than placebo ($p<0.05$)

4.8 *Subgroup analysis*

4.8.1 *Methods*

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

- Age group (<65 years, ≥65 years)
- Gender (male, female)
- Race (white, black, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Baseline BMI (<30 kg/m^2, ≥30 kg/m^2)
- HCV sub-genotype
- Cirrhosis (presence, absence, missing)
- IL28B genotype (CC, non-CC)
- 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 (DAA+Peg-IFN+RBV, Peg-IFN+RBV, other)
- Prior HCV treatment response (non-responder, relapse/breakthrough)

In addition, ASTRAL-1 and ASTRAL-3 also included the following subgroup

- Region (US, non-US)

4.8.2 *Results*

ASTRAL-3 (HCV GT3)

Across the 2 treatments groups, SVR12 rates consistently favoured the SOF/VEL 12 week group over the SOF+RBV 24 week group for the treatment of patients with HCV GT2 infection. In particular, SVR rates with SOF/VEL 12 weeks were relatively consistent irrespective of cirrhotic status or prior treatment experience with SVR12 rates ranging from 89.2% to 98.2%. By contrast, there were notable differences in SVR12 rates for patients treated with SOF+RBV for 24 weeks with the highest rate being 91.0% in HCV treatment-naïve patients without cirrhosis and the lowest being 57.9% in patients with prior treatment experience and cirrhosis. SVR12 rates by cirrhotic status and prior HCV treatment experience are summarised below. Tabulated results for all subgroups are provided in Appendix 5.

By cirrhotic status

- Without cirrhosis: 97.0% SOF/VEL versus 87.7% SOF+RBV
- With cirrhosis: 91.3% SOF/VEL versus 66.3% SOF+RBV

By prior treatment experience

- Treatment-naïve: 97.1% SOF/VEL versus 86.8% SOF+RBV
- Treatment-experienced: 90.1% SOF/VEL versus 63.4% SOF+RBV

By cirrhotic status and prior treatment experience

- Treatment-naïve without cirrhosis: 98.2% SOF/VEL versus 91.0% SOF+RBV
- Treatment-naïve with cirrhosis: 93.0% SOF/VEL versus 73.3% SOF+RBV
- Treatment-experienced without cirrhosis: 91.2% SOF/VEL versus 71.0% SOF+RBV
- Treatment-experienced with cirrhosis: 89.2% SOF/VEL versus 57.9% SOF+RBV

ASTRAL-2 (HCV GT2)

The high SVR12 rates observed in both treatment groups in patients with HCV GT2 infection, with no cases of virologic failure in the SOF/VEL 12 week group (n=134) and six cases of virologic failure in the SOF+RBV 12 week group (n=132), precluded meaningful interpretation of subgroup analyses. The prognostic factors that have been traditionally predictive of or associated with lower rates of SVR, such as cirrhosis, high BMI, high viral load, non-CC IL28B allele had no impact on SVR12 rates. SVR12 rates by cirrhotic status and prior HCV treatment experience are summarised below. Tabulated results for all subgroups are provided in Appendix 5.

By cirrhotic status

- Without cirrhosis: 99.1% SOF/VEL versus 93.8% SOF+RBV
- With cirrhosis: 100.0% SOF/VEL versus 94.7% SOF+RBV

By prior treatment experience

- Treatment-naïve: 99.1% SOF/VEL versus 95.5% SOF+RBV
- Treatment-experienced: 100.0% SOF/VEL versus 85.0% SOF+RBV

By cirrhotic status and prior treatment experience

- Treatment-naïve without cirrhosis: 99.0% SOF/VEL versus 95.8% SOF+RBV
- Treatment-naïve with cirrhosis: 100.0% SOF/VEL versus 93.3% SOF+RBV
- Treatment-experienced without cirrhosis: 100.0% SOF/VEL versus 81.3% SOF+RBV
- Treatment-experienced with cirrhosis: 100.0% SOF/VEL versus 100.0% SOF+RBV

ASTRAL-1 (HCV GT1, GT2, GT4–6)

In ASTRAL-1, high SVR12 rates were achieved with SOF/VEL for 12 weeks in all subgroups across all HCV genotypes, including those with cirrhosis (99%) and prior treatment experience (>99%).

SVR12 rates by cirrhotic status and prior HCV treatment experience are summarised below. Tabulated results for all subgroups are provided in Appendix 5.

By cirrhotic status

- Without cirrhosis: 99.0%
- With cirrhosis: 99.2%

By prior treatment experience

- Treatment-naïve: 98.8%
- Treatment-experienced: 99.5%

- All patients previously treated previously with a DAA+Peg-IFN+RBV achieved SVR12 (56/56), which included 48, six, and two patients with HCV GT1, GT4, and GT5 infection, respectively.

4.9 *Meta-analysis*

Not applicable

4.10 *Indirect and mixed treatment comparisons*

4.10.1 *Overview*

The SOF/VEL studies described in Section 4.3 (ASTRAL-1, -2, -3) and 4.10.9.1 (ASTRAL-4, ELECTRON-2, Everson et al, 2015 and Pianko et al, 2015) provide some direct evidence of comparative effectiveness versus comparators of relevance to current clinical practice – ASTRAL-3 in CHC GT3 versus SOF+RBV for 24 weeks and ASTRAL-2 in CHC GT2 versus SOF+RBV for 12 weeks.

However, given the large number of treatment regimens available for CHC it is impractical to design trials that compare with all potential comparators, nor to design pangenotypic trials versus a single standard of care. At the time of the design of the ASTRAL programme it would not have been clear that there was a definitive standard of care regimen for each disease progression state with which to compare. Where a standard of care was possible to define (in GT2 and GT3) the ASTRAL trials were designed to reflect this. Comparing against more than one other comparator in a Phase III trial, using either a non-inferiority or superiority design is: methodologically difficult; would require very large patient numbers to adequately power; would likely require a follow-up period that was so long that the standard of care would be obsolete by the time the study had enrolled due to the concurrent development of DAA combinations from multiple manufacturers.

To estimate relative efficacy of SOF/VEL versus all comparators defined in the NICE scope for this appraisal, the feasibility of undertaking an NMA was explored, as described in Section 4.10.2 onwards. Evidence networks could only be constructed for populations of patients with CHC GT1 who were treatment-naïve and those with CHC GT3 who were treatment-naïve. Evidence networks could not be constructed for GT1 treatment-experienced or any patients with CHC GT2, GT4, GT5 or GT6. While a small network in GT3 treatment-experienced for some relevant interventions was technically feasible, this was not explored further for use in the economic analysis, as described in Section 4.10.8. In addition, the results from the NMA for GT3 treatment-naïve and GT1 treatment-naïve were associated with a number of limitations, as described in Section 4.10.8, and were therefore not considered robust enough to populate the economic analysis.

The approach taken to source efficacy data for comparators across all genotypes was therefore one of naïve comparison, taking data from an individual study or studies across all patient groups. Given the limitations of the NMA, the naïve comparison represents a more transparent approach to evidence comparison in this instance. Furthermore, all studies use SVR as the primary efficacy endpoint, a hard endpoint which does not require subjective assessment and which is consistently measured across studies.

Study identification strategy is described in Section 4.10.2, with subsequent NMA study selection, networks, methodology and results described in Section 4.10.3 through 4.10.7.

Studies selected for naïve comparisons are described in Section 4.10.9.

4.10.2 *NMA search strategy and study selection*

A systematic review was performed to identify randomised comparative evidence for SOF/VEL and comparators of relevance to the NICE scope for this appraisal, with the aim of building an evidence network for treatment comparison. The methods of the review have been described in Section 4.1.

A total of 89 publications and 10 conference abstracts were identified by the systematic review (reporting on 100 studies). Sixty publications and 10 conference abstracts (total of 70 publications/abstracts covering 71 studies) reported on randomised comparisons between the interventions listed in Table 9, including SOF/VEL and comparators identified in the NICE scope for this appraisal, and were used to assess the feasibility of performing an NMA. All 71 studies are listed in Table 31.

A further 29 publications assessed randomised comparisons of Peg-IFN+RBV regimens only. Given the rapid evolution of the CHC treatment field and the use of Peg-IFN+RBV as a comparator arm in many DAA studies, these Peg-IFN only studies were not included in evidence networks and were only considered further in the event of data gaps and inability to complete an evidence network. All 29 Peg-IFN only studies are listed in Appendix 6.

Table 31: Randomised studies identified by the systematic review

Study ID	Primary publication	Associated publications
SOF/VEL studies		
ASTRAL-1	Feld 2015 (70)	-
ASTRAL-2	Foster 2015 (28)	-
ASTRAL-3	Foster 2015 (28)	-
ASTRAL-4	Curry 2015 (71)	-
Comparator studies		
ADVANCE	Jacobson 2011 (79)	-
AI444-031	Dore 2015 (80)	-
AI444040	Sulkowski 2014 (81)	-
ALLY-2	Wyles 2015 (82)	-
ASPIRE	Zeuzem 2014 (83)	-
ATOMIC	Kowdley 2013 (84)	-
ATTAIN	Reddy 2015 (85)	-
BOSON	Foster 2015 (86)	-
C210	Benhamou 2013 (87)	-
Chulanov AASLD 2014	Chulanov AASLD 2014 (88)	-
COMMAND-1	Hezode 2015 (89)	-
COMMAND-4	Hezode 2015 (90)	-

Study ID	Primary publication	Associated publications
COSMOS	Lawitz 2014 (91)	-
C-SWIFT	Poordad EASL 2015 (92)	-
C-WORTHY	Sulkowski 2015 (93)	Lawitz 2015 (94)
ELECTRON	Gane 2013 (30)	-
ELECTRON-2	Gane AASLD 2014 (74)	-
Everson 2015	Everson 2015 (73)	-
FISSION	Lawitz 2013 b (19)	-
Flamm 2013	Flamm 2013 (95)	-
Flamm AASLD 2014	Flamm AASLD 2014 (96)	-
Foster 2011	Foster 2011 (97)	-
FUSION	Jacobson 2013 (31)	-
Gane 2015	Gane 2015 (98)	Gane EASL 2014 (99)
ILLUMINATE	Sherman 2011 (100)	-
ION-1	Afdhal 2014 (101)	-
ION-2	Afdhal 2014 (102)	-
ION-3	Kowdley 2014 (27)	-
LEAGUE-1	Zeuzem 2016 (103)	-
LONESTAR	Lawitz 2014 (104)	-
MALACHITE-I	Dore 2015 (105)	-
MALACHITE-II	Dore 2015 (105)	-
Manns 2014	Manns 2014 (106)	-
Marcellin 2011	Marcellin 2011 (107)	-
OPERA-1	Manns 2011 (108)	-
OPTIMIST-1	Kwo EASL 2015 (109)	-
PEARL-I	Hezode 2015 (110)	-
PEARL-II	Andreone 2014 (111)	-
PEARL-III	Ferenci 2014 (112)	-
PEARL-IV	Ferenci 2014 (112)	-
Pianko 2015	Pianko 2015 (72)	-
PILLAR	Fried 2013 (113)	-
Pol 2012-	Pol 2012 (114)	-
POSITRON	Jacobson 2013 (31)	-
PROMISE	Forns 2014 (115)	-
PROTON	Lawitz 2013 a (116)	-
PROVE-1	McHutchison 2009 (117)	-
PROVE-2	Hezode 2009 (118)	-
PROVE-3	McHutchison 2010 (119)	-

Study ID	Primary publication	Associated publications
QUEST-1	Jacobson 2014 (120)	-
QUEST-2	Manns 2014 (121)	-
REALIZE	Zeuzem 2011 (122)	-
RESPOND-2	Bacon 2011 (123)	-
Rodriguez-Torres 2013	Rodriguez-Torres 2013 (124)	-
SAPPHIRE-I	Feld 2014 (125)	-
SAPPHIRE-II	Zeuzem 2014 (126)	-
SIRIUS	Bourliere 2015 (127)	-
SOLAR-1	Charlton 2015 (128)	-
SOLAR-2	Manns EASL 2015 (129)	-
SPRINT-1	Kwo 2010 (130)	-
SPRINT-2	Poordad 2011 (131)	-
STOP C	Basu AASLD 2014 (132)	Basu EASL 2015 (133)
Sulkowski 2013	Sulkowski 2013 (134)	-
Sulkowski 2013	Sulkowski 2013 (135)	-
TURQUOISE-I	Sulkowski 2015 (136)	-
TURQUOISE-II	Poordad 2014 (137)	-
Vierling EASL 2015	Vierling EASL 2015 (138)	-

4.10.3 *Trials used to inform the NMA*

All studies included from the systematic review were considered for inclusion in the NMA. The evidence only allowed two evidence networks to be formed for which NMA could be performed:

- Patients with CHC GT3 who were treatment-naïve
- Patients with CHC GT1 who were treatment-naïve

For all other populations based on genotype and prior treatment experience, evidence networks could not be formed which would allow a NMA to be performed. Further information on these populations is provided in Section 4.10.3.3.

A list of studies included in final evidence networks with relevant treatment arms and SVR data are presented in Table 32 and Table 33 for the GT3 and GT1 treatment-naïve networks, respectively. Evidence network diagrams are presented in Section 4.10.3.1 for GT3 treatment-naïve and Section 4.10.3.2 for GT1 treatment-naïve.

In addition, data from a study which compared Peg-IFN+RBV with placebo (Zeuzem, 2004 (139)) had to be used to connect SOF12+VEL12 to the main network. This study was not identified in the systematic review because of the 2006 date cut off applied, but was deemed the most appropriate to complete the evidence network, as outlined in Section 4.10.3.2.

For ease of reporting each treatment has been assigned a three letter code (see abbreviations table), and the treatment duration of the individual components are then given after this code. For example, SOF and VEL given for 12 weeks would be SOF12+VEL12.

In cases where treatments were response-guided and different patients could thus receive treatment for different durations, a '/' was used to separate the treatment durations. For example, if patients received DCV and SMV for 12 or 24 weeks, the abbreviation would be DCV12/24+SMV12/24.

A number of studies reported efficacy data for i) Peg-IFN 2a and/or 2b in combination with other treatments and ii) Peg-IFN+RBV. These drugs were also administered in varying durations (4–48 weeks) in these studies. Due to the emergence of DAAs, the use of these IFN-containing regimens independently has reduced and estimating the relative efficacy of these IFN-containing regimens was not considered relevant to the decision problem. In light of this, the following assumptions were made for the NMA:

- Peg-IFN 2a and Peg-IFN 2b have equivalent efficacy in terms of SVR12.
- Peg-IFN 2a/Peg-IFN 2b in combination with RBV have equivalent efficacy in terms of SVR12 regardless of treatment duration.

All Peg-IFN and RBV-containing regimens were hence pooled into one treatment (Peg-IFN+RBV). These assumptions were validated by a clinical expert and the impact of pooling durations was explored in a sensitivity analysis (Section 4.10.7.2). It should be noted that this assumption had little impact in GT3 treatment-naïve populations, where all studies utilising Peg-IFN+RBV as a treatment arm used 24 weeks of treatment. Studies identified in the systematic review which only investigated Peg-IFN+RBV (as listed in Appendix 6) were not included in the evidence networks.

Table 32: Input data for SVR – GT3 treatment-naïve

Study	Treatment	N	n	%
AI444-031 (80)	DCV12+Peg-IFN+RBV	26	18	69.2
	DCV16+Peg-IFN+RBV	27	21	77.8
	Peg-IFN+RBV	27	14	51.9
ASTRAL-3 (28)	SOF24+RBV24	204	176	86.3
	SOF12+VEL12	206	200	97.1
BOSON (86)	SOF24+RBV24	94	83	88
	SOF12+Peg-IFN+RBV	94	89	95
	SOF16+RBV16	91	70	77
Chulanov AASLD (2014) (88)	SOF24+RBV24	31	28	90
	SOF16+RBV16	30	26	87
ELECTRON (30)	SOF12+Peg-IFN+RBV	7	6.5	100
	SOF12+Peg-IFN+RBV	6	5.5	100
	SOF12+Peg-IFN+RBV	6	5.5	100
	SOF12+RBV12	6	5.5	100
FISSION (19)	Peg-IFN+RBV	176	110	62.5

Study	Treatment	N	n	%
	SOF12+RBV12	183	102	55.7
Foster (2011) (97)	Peg-IFN+RBV	9	4	44
	TVR2+Peg-IFN+RBV	9	6	67
	TVR2mono+Peg-IFN+RBV	8	4	50

BOC, boceprevir; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; PBO, placebo; Peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; VEL, velpatasvir.
Trials with multiple arms reporting the same treatments reflect the Peg-IFN+RBV duration pooling assumption. Hence treatment durations are not included for Peg-IFN+RBV containing regimens.

Table 33: Input data for SVR – GT1 treatment-naïve

Study	Treatment	N	n	%
ADVANCE (79)	Peg-IFN+RBV	361	158	43.8
	TVR12+Peg-IFN+RBV	363	271	74.7
	TVR8+Peg-IFN+RBV	364	250	68.7
ASTRAL-1 (70)	PBO12	46	0	0
	SOF12+VEL12	218	214	98.2
ATOMIC (84)	SOF12+Peg-IFN+RBV	52	47	90.4
	SOF24+Peg-IFN+RBV	155	141	91
	SOF24+Peg-IFN+RBV	109	101	92.7
COMMAND-1 (90)	Peg-IFN+RBV	72	26	36.1
	DCV12/24+Peg-IFN+RBV	146	88	60.3
Lawitz (2013) (116)	Peg-IFN+RBV	26	15	58
	SOF12+Peg-IFN+RBV	47	43	91
MALACHITE-I (105)	OBV12+PTV12+RTV12+DSV12	83	81	98
	OBV12+PTV12+RTV12+DSV12+ RBV12	69	67	97
	OBV12+PTV12+RTV12+DSV12+RBV12	84	83	99
	TVR12+Peg-IFN+RBV	34	28	82
	TVR12+Peg-IFN+RBV	41	32	78
Manns (2014) (106)	BOC24+Peg-IFN+RBV	66	40	61
	GZR12+Peg-IFN+RBV	66	59	89
PEARL-III (112)	OBV12+PTV12+RTV12+DSV12	209	207	99
	OBV12+PTV12+RTV12+DSV12+RBV12	210	209	99.5
PEARL-IV (112)	OBV12+PTV12+RTV12+DSV12	205	185	90.2
	OBV12+PTV12+RTV12+DSV12+RBV12	100	97	97
PILLAR (113)	Peg-IFN+RBV	77	51	66.2
	SMV12+Peg-IFN+RBV	77	62	80.5
	SMV24+Peg-IFN+RBV	79	68	86.1

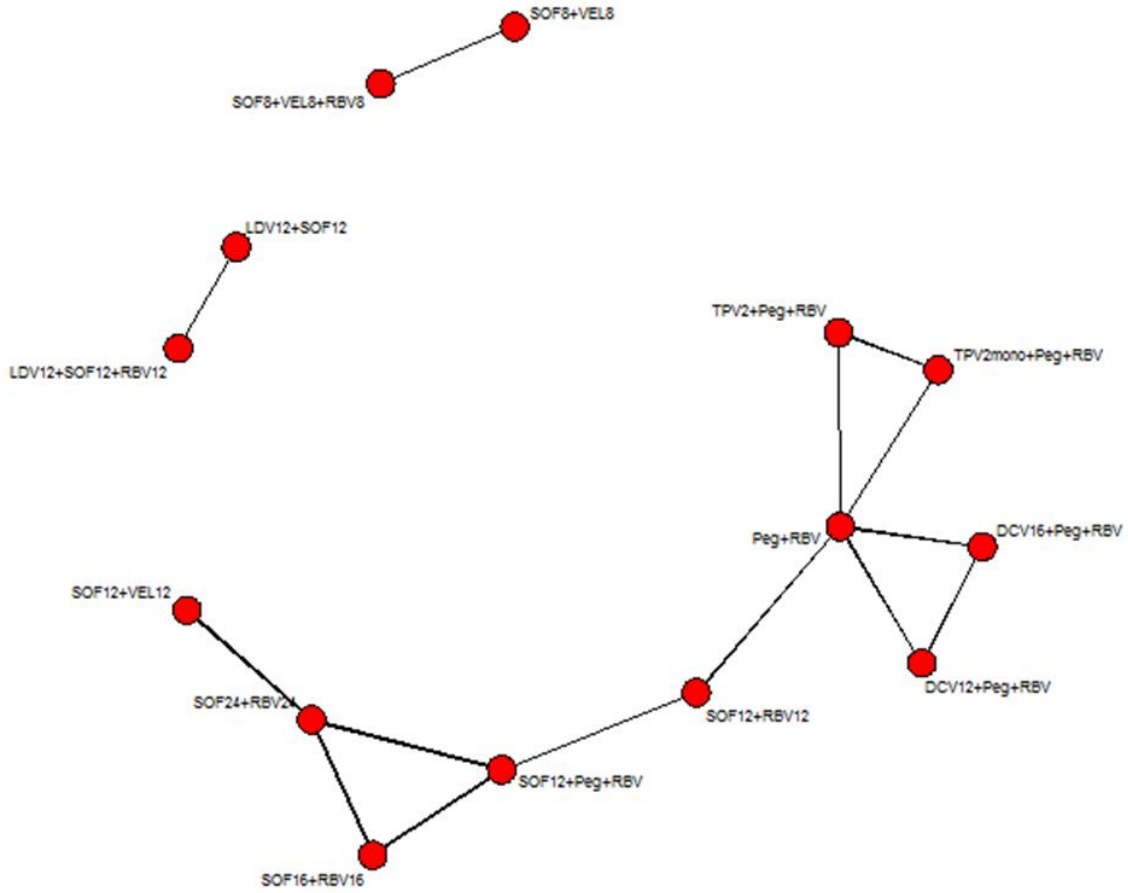
Study	Treatment	N	n	%
Pol (2012) (114)	Peg-IFN+RBV	12	3	25
	DCV48+Peg-IFN+RBV	12	10	83
PROVE-2 (118)	Peg-IFN+RBV	82	38	46.3
	TVR12+Peg-IFN	78	28	35.9
	TVR12+Peg-IFN+RBV	82	49	59.8
	TVR12+Peg-IFN+RBV	81	56	69.1
PROVE-1 (117)	Peg-IFN+RBV	75	31	41
	TVR12+Peg-IFN+RBV	17	6	35
	TVR12+Peg-IFN+RBV	79	48	61
	TVR12+Peg-IFN+RBV	79	53	67
QUEST-1 (120)	Peg-IFN+RBV	130	65	50
	SMV12+Peg-IFN+RBV	264	210	80
QUEST-2 (121)	Peg-IFN+RBV	134	67	50
	SMV12+Peg-IFN+RBV	257	209	81
Rodriguez-Torres (2013) (124)	Peg-IFN+RBV	14	7	50
	SOF4+Peg-IFN+RBV	15	13	87
SPRINT-1 (130)	Peg-IFN+RBV	104	39	37.5
	BOC24+Peg-IFN+RBV	103	58	56.3
	BOC28+Peg-IFN+RBV	107	58	54.2
	BOC44+Peg-IFN+RBV	103	77	74.8
	BOC48+Peg-IFN+RBV	103	69	67
SPRINT-2 (131)	Peg-IFN+RBV	363	137	37.7
	BOC24+Peg-IFN+RBV	368	233	63.3
	BOC44+Peg-IFN+RBV	366	242	66.1
TURQUOISE-II (137)	OBV12+PTV12+RTV12+DSV12+RBV12	86	81	94.19
	OBV24+PTV24+RTV24+DSV24+RBV24	74	70	94.59
Zeuzem (2004) (139)	Peg-IFN+RBV	144	19.5	13
	Peg-IFN+RBV	141	57.5	40
	PBO12	47	0.5	0

BOC, boceprevir; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; PBO, placebo; Peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; VEL, velpatasvir.
Trials with multiple arms reporting the same treatments reflect the Peg-IFN+RBV duration pooling assumption. Hence treatment durations are not included for Peg-IFN+RBV containing regimens.

4.10.3.1 GT3 treatment-naïve

The network of studies reporting SVR for GT3 treatment-naïve is presented in Figure 6.

Figure 6: Network of evidence for SVR – GT3 treatment-naïve



Refer to Table 32 for intervention names and abbreviations.

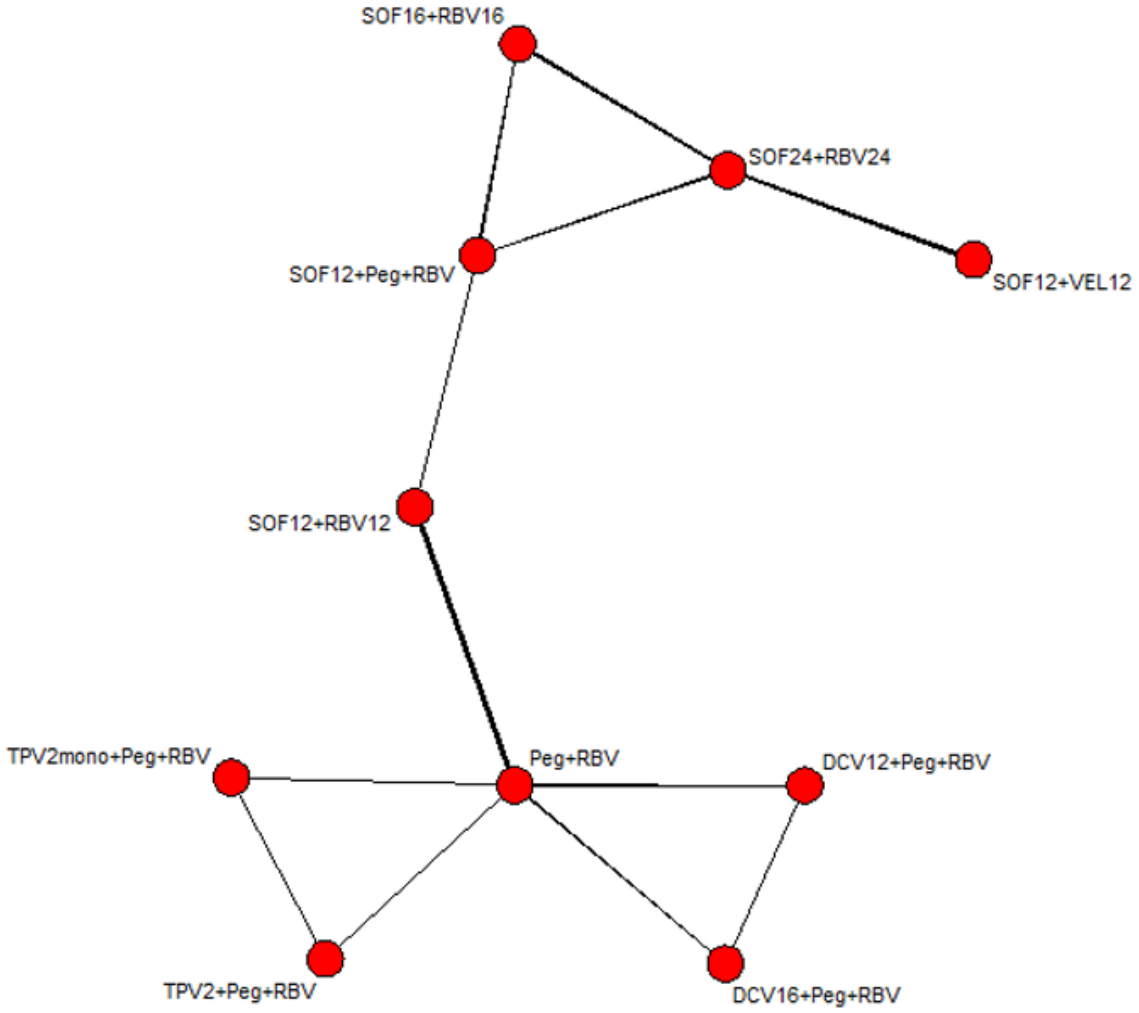
Two studies identified by the systematic review provided GT3 treatment-naïve data but were disconnected from the main network:

- Gane (2015) (98); assessed the efficacy of LDV12+SOF12+RBV12 compared with LDV12+SOF12
- ELECTRON-2 (74); assessed the efficacy of SOF8+VEL8+RBV8 compared with SOF8+VEL8

Both studies were therefore excluded from the analysis (Table 36).

The final network is presented in Figure 7.

Figure 7: Final network of evidence for SVR – GT3 treatment-naïve

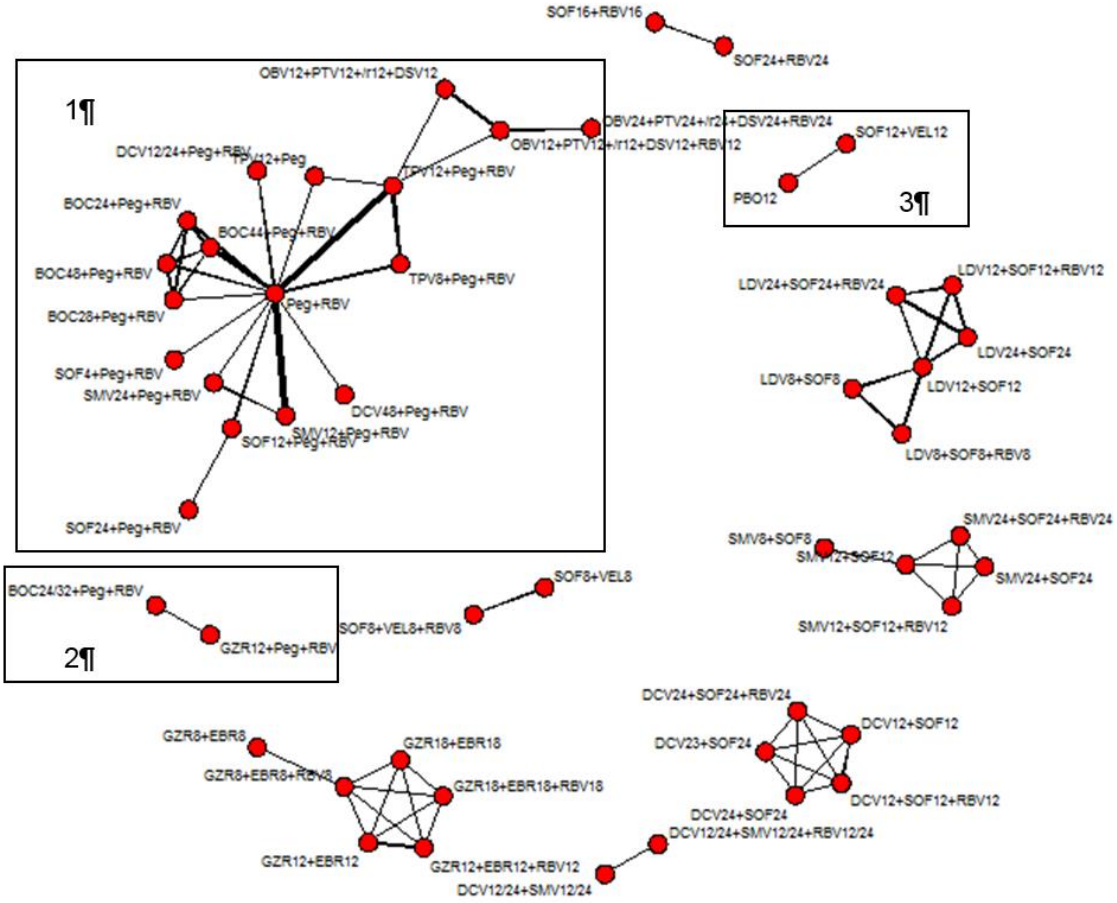


Refer to Table 32 for intervention names and abbreviations.

4.10.3.2 GT1 treatment-naïve

The network of studies reporting SVR data in GT1 treatment-naïve patients is presented in Figure 8. The thickness of the line connecting any two treatments is proportional to the number of patients informing that comparison.

Figure 8: Network of evidence for SVR – GT1 treatment-naïve



Refer to Table 33 for intervention names and abbreviations.

Thirteen studies identified by the systematic review provided GT1 treatment-naïve data but were disconnected from the main network which links through Peg-IFN+RBV depicted in Figure 8, box 1. Two of the disconnected studies were considered to be important for estimating relative efficacy of SOF/VEL versus comparator regimens:

- Manns 2014 (106) assessed the efficacy of response-guided therapy of BOC24/32+Peg28/48+RBV28/48 compared with GZR12+Peg24/48+RBV24/48 (box 2)
- ASTRAL-1 (70); assessed the efficacy of SOF12+VEL12 compared with placebo (box 3)

Given that ASTRAL-1 is the only study reporting SVR data for SOF12+VEL12 in GT1 treatment-naïve, it was necessary to connect this study to the main network.

The assumptions made to connect these studies to the network are presented in Table 34. Both assumptions were validated by a clinical expert at Gilead. To connect ASTRAL-1 to the GT1 treatment-naïve network, an assumption of equivalent efficacy was made between placebo and no treatment from the Zeuzem 2004 (139) study (blue line on Figure 9). This was considered to be clinically plausible as patients who do not receive treatment and patients on placebo alone are not expected to achieve SVR. This was observed in the ASTRAL-1 study and the POSITRON study (31) where 0% of patients on placebo achieved SVR.

Table 34: Assumptions to connect the network

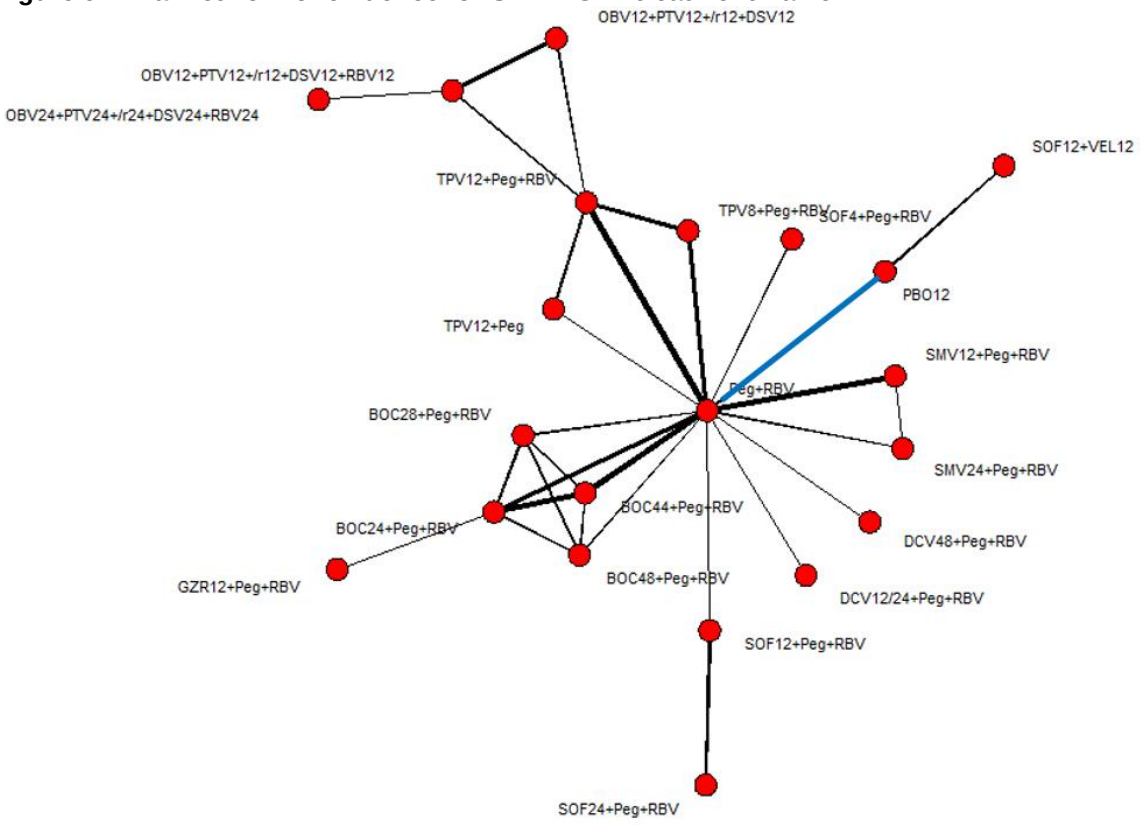
Study	Disconnected treatments	Method for generating connection to main network
Manns 2014 (106)	GZR12+Peg-IFN+RBV BOC24/32+Peg-IFN+RBV	BOC24/32+Peg-IFN+RBV and BOC24+Peg-IFN+RBV were assumed to have equivalent efficacy in terms of SVR12
ASTRAL-1 (70)	PBO12 SOF12+VEL12	The Zeuzem 2004 study (139) compared Peg-IFN+RBV with 'no treatment' and was identified in a systematic literature review that was conducted in support of a previous STA submission to NICE. This study had not been included in our review given i) the date restriction posed on the literature searches and ii) we excluded studies which compared Peg-IFN and RBV alone. The 'no treatment' arm was utilised as a proxy for PBO.

BOC, boceprevir; GZR, grazoprevir; PBO, placebo; Peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

The remaining eleven studies were excluded from the analysis (Table 37).

The final network is presented in Figure 9.

Figure 9: Final network of evidence for SVR – GT1 treatment-naïve



Refer to Table 33 for intervention names and abbreviations.

4.10.3.3 Other populations

Evidence networks for NMA could not be formed for the formed for the remaining populations of relevance to the decision problem, namely treatment-experienced patients with GT1/2/3/4/5/6 infection and treatment-naïve patients with GT2/4/5/6 infection.

NMA feasibility conclusions are summarised in Table 35 and evidence networks for each population are provided in Appendix 7.

Table 35: NMA feasibility conclusions for other populations

Population	Comments
GT2 TN	• No data (three disconnected studies)
GT4 TN	• No data (three disconnected studies)
GT5 TN	• No studies
GT6 TN	• No data (one study)
GT4, 5 and 6 TN	• No data (three disconnected studies)
GT1 TE	• Unable to connect SOF12+VEL12 to the main network; the Zeuzem 2004 study (139) is no longer able to connect the ASTRAL-1 study through placebo as Zeuzem 2004 is exclusively in a TN population
GT2 TE	• No data (three disconnected studies)
GT3 TE	• Small network (See Section 4.10.8 for further discussion)
GT4 TE	• No data (one study)
GT5 TE	• No studies
GT6 TE	• No data (one study)
GT4, 5 and 6 TE	• No data (one study)
All genotypes TE	• Small networks of 6 treatments • SOF12+VEL12 disconnected

GT, genotype; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir.

4.10.4 *Studies excluded from the analysis*

Studies identified in the systematic review which provided GT3 or GT1 treatment-naïve data but could not be included in the network are shown in Table 36 and Table 37, respectively, accompanied by reason(s) for exclusion.

The remaining studies identified in the review were excluded because they did not include disaggregated data for GT3 or GT1 treatment-naïve CHC, nor did they allow formation of evidence networks for the other populations described in Section 4.10.3.3, and are listed in Appendix 7.

Table 36: Study arms excluded from NMA – GT3 treatment-naïve

Study ID	Arms/interventions	Reason for exclusion
ELECTRON-2	SOF8+VEL8	Disconnected from main network
	SOF8+VEL8+RBV8	
Gane 2015	LDV12+SOF12	Disconnected from main network

	LDV12+SOF12+RBV12	

LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

Table 37: Study arms excluded from NMA – GT1 treatment-naïve

Study ID	Arms/interventions	Reason for exclusion
AI444040	DCV23+SOF24	Disconnected from main network
	DCV24+SOF24	
	DCV24+SOF24+RBV24	
	DCV12+SOF12	
	DCV12+SOF12+RBV12	
Chulanov AASLD 2014	SOF16+RBV16	Disconnected from main network
	SOF24+RBV24	
COSMOS	SMV24+SOF24+RBV24	Disconnected from main network
	SMV24+SOF24	
	SMV12+SOF12+RBV12	
	SMV12+SOF12	
C-SWIFT	SOF4+GZR4+EBR4	Does not report SVR data
	SOF6+GZR6+EBR6	
	SOF6+GZR6+EBR6	
	SOF8+GZR8+EBR8	
C-WORTHY	GZR8+EBR8+RBV8	Disconnected from main network
	GZR12+EBR12	
	GZR12+EBR12+RBV12	
	GZR12+EBR12	
	GZR18+EBR18+RBV18	
	GZR18+EBR18	
Everson 2015	SOF8+VEL8	Disconnected from main network
	SOF8+VEL8+RBV8	
ILLUMINATE	TVR12+Peg-IFN24+RBV24	Collapses into one treatment arm
	TVR12+Peg-IFN48+RBV48	
	TVR12+Peg-IFN48+RBV48 (no eRVR)	
ION-1	LDV12+SOF12	Disconnected from main network
	LDV12+SOF12+RBV12	
	LDV24+SOF24	
	LDV24+SOF24+RBV24	
ION-3	LDV8+SOF8	Disconnected from main network
	LDV8+SOF8+RBV8	
	LDV12+SOF12	

Study ID	Arms/interventions	Reason for exclusion
LEAGUE-1	DCV12/24+SMV12/24	Disconnected from main network
	DCV12/24+SMV12/24+RBV12/24	
LONESTAR	SOF8+LDV8	Disconnected from main network
	SOF8+LDV8+RBV8	
	SOF12+LDV12	
Marcellin 2011	TVR12(750 mg)+Peg-IFN2a+RBV	Collapses into one treatment arm
	TVR12(750 mg)+Peg-IFN2b+RBV	
	TVR12(1125 mg)+Peg-IFN2a+RBV	
	TVR12(1125 mg)+Peg-IFN2b+RBV	
OPTIMIST-1	SMV12+SOF12	Disconnected from main network
	SMV8+SOF8	
Vierling EASL 2015	GZR8+EBR8+RBV8	Disconnected from main network
	GZR8+EBR8	

BOC, boceprevir; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; PBO, placebo; Peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; VEL, velpatasvir.

4.10.5 *Methods and outcomes of studies included in NMA*

SVR was the single endpoint analysed in the NMA. SVR data were extracted as binary data, i.e. the number and proportion of patients experiencing SVR were extracted. SVR data for the included studies are provided in Table 32 and Table 33.

SVR was defined as viral response at the end of treatment that was sustained at 12 weeks post-treatment (SVR12). SVR24 data were also extracted if available, defined as viral response at the end of treatment sustained at 24 weeks post-treatment. SVR12 and SVR24 were assumed to be equivalent for the purposes of the NMA given the high concordance between these outcomes (14). Data for SVR12 were used by default; data for SVR24 were used where SVR12 was not reported.

Studies defined SVR as HCV RNA levels below a specified level at post-treatment week 12 or 24; this level ranged between 10 IU/mL and 25 IU/mL. These cut-offs were considered to be equivalent for the purposes of the NMA (140).

Upon reviewing the disease and patient baseline characteristics extracted from the included studies, the studies were deemed to be generally homogeneous with the exception of METAVIR score, which is known to be a significant treatment effect modifier (14). This was also discussed and validated by external clinical expert opinion (please see Section 5.3.3). As METAVIR has such an impact on outcomes, the following subgroup analyses were thus considered to explore the impact of METAVIR score:

- METAVIR score F4 (cirrhotic)
- METAVIR score F0-F3 (non-cirrhotic)

However, upon reviewing the networks for these subgroups, it was concluded that these could not be robustly analysed due to the number of disconnections around the treatments of interest. Further discussion is provided in Section 4.10.8.

4.10.6 *Methods of NMA*

4.10.6.1 Input data

The input data comprised the total number of patients (N) and the number of patients who achieved SVR12/SVR24 (n) in a given treatment arm. The systematic review extracted N by ITT, modified ITT and endpoint-specific populations where reported.

In instances where data were missing, it was necessary to impute values to enable the corresponding studies to be included in the analysis.

Where n was missing but the proportion was reported, n was calculated by applying the proportion of patients experiencing the event of interest to the endpoint-specific N.

4.10.6.2 Models

The underlying model for an NMA is a generalised linear model (141) where linear combinations of predictor variables are related to endpoints. The endpoints modelled can include continuous and binary variables, and are assumed to be derived from an underlying distribution that is chosen based on the type of endpoint. A link function is then specified to map the linear combination to the endpoint. The structure of an NMA therefore differs according to the type of endpoint being modelled.

Given the input data for this analysis are binary (number of patients achieving SVR out of the total number of patients in each treatment arm) and the parameters of interest are probabilities (probability of achieving SVR on a given treatment), these data would typically be analysed on the log odds scale, using a logit link function (141). However the evidence base contains some treatment arms in which the proportion of patients achieving SVR is zero (0%) or one (100%), which hence lie at the boundary of the probability scale. This can present problems for methods of synthesis on the log-odds scale, because the log odds are infinite.

In light of this, analyses were conducted on both the log-odds and absolute risk scales. Therefore, four analyses were considered for each network:

- Log-odds scale, with relative treatment effects reported as log odds ratios, fixed and random effects, with a continuity correction of +0.5 events to arms in trials with 0 counts and -0.5 for arms in trials with 100% counts
- Absolute risk scale, with relative treatment effects reported as absolute risk differences, fixed and random effects

Table 38: Summary of analyses

Scale	Quantification of relative treatment effects	Fixed effects	Random effects
Log odds	Log-odds ratios	✓	✓
Absolute risk	Absolute risk differences	✓	✓

Log-odds scale

Observed data are included in the model using a binomial likelihood where the probability (p) of response for study i and treatment k is as follows:

$$r_{i,k} \sim \text{Binomial}(p_{i,k}, n_{i,k})$$

where $r_{i,k}$ is the number of events in treatment arm k of study i, and $n_{i,k}$ is the total number of patients in treatment arm k of study i.

Treatments k included in the model will be indexed as positive integers with the baseline treatment (b) being the lowest index treatment in study i. A logit link function is used to map the probability of response to the linear model such that for treatment arm k of study i:

$$\text{logit}(p_{i,k}) = \alpha_i + (\beta_{i,k} - \beta_{i,b})$$

where α_i is the study-specific baseline term, and $\beta_{i,k} - \beta_{i,b}$ is the study-specific log odds ratio of treatment k compared with baseline b for the fixed effect model. For study arms receiving the baseline treatment (i.e. $k = b$), this simplifies to the study-specific baseline term α_i.

The corresponding random effects model replaces the constant treatment effect with the study-specific treatment effect $\delta_{i,k}$. This is normally distributed with mean $mb_{i,k} = (\beta_{i,k} - \beta_{i,b})$ and variance σ^2, where σ^2 is the random effects variance and assumed to be constant across all treatment comparisons. (Note that this model will be equivalent to a fixed effect model when $\sigma^2 = 0$). The following changes are made for the random effects model:

$$\text{logit}(p_{i,k}) = \alpha_i + \delta_{i,k}$$

$$\delta_{i,k} \sim N(mb_{i,k}, \sigma^2)$$

$$mb_{i,k} = (\beta_{i,k} - \beta_{i,b})$$

The parameters of interest modelled are the log odds ratios (β) which represent the relative effect of each treatment compared with the reference treatment in the analysis. Relative treatment effects can also be derived on the risk difference scale (141). Estimates of these parameters are iteratively sampled using Bayesian methods. The parameter value can be summarised by calculating the mean and standard error of these samples (i.e. mean log odds ratio and corresponding standard error, which can be converted to odds ratios). In addition, the credible interval (CrI) can be estimated from these samples. These are similar to CI in a Frequentist analysis, but the interpretation differs as described below for a 5% significance level:

- Frequentist 95% CI: 95% probability that the true value lies within 95% of these intervals in the long run, if many samples were taken of the data.
- Bayesian 95% CrI: 95% probability that the true value of the parameter lies within the interval.

The 95% CrI in a Bayesian analysis are the values corresponding to the lower 2.5 and upper 97.5 percentiles of samples taken for each parameter modelled (141).

Absolute risk scale

Observed data are included in the model using a binomial likelihood, the same as when using the log-odds scale. However, in this approach the probability of response for treatment arm k of study i is estimated directly as a linear function of the basis parameters rather than as a logit function:

$$p_{i,k} = \alpha_i + \beta_k$$

where α_i is the study-specific baseline term representing the response to the reference treatment, and β_k is the absolute difference in the probability of response for treatment k compared with the reference treatment.

The corresponding random effects model effectively replaces the constant treatment effect with the study-specific treatment effect $\delta_{i,k}$ as follows:

$$p_{i,k} = \alpha_i + \delta_{i,k}$$

$$\delta_{i,k} \sim N(\beta_k, \sigma^2)$$

The parameters of interest modelled are the risk (probability) differences (β) which represent the relative effect of each treatment compared with the reference treatment in the analysis. Estimates of these parameters are iteratively sampled using Bayesian methods and the CrI estimated from these samples are as per the log-odds scale.

An arm-based parameterisation was used for the risk differences model, hence no modifications to the code were required to adjust for multi-arm trials (142).

4.10.6.3 Reference treatment

For both the GT3 and GT1 treatment-naïve analyses Peg-IFN+RBV was selected as the reference treatment given this represents a historical standard of care in CHC (143) and is the most commonly reported treatment in this dataset.

4.10.6.4 Prior distributions

The evidence synthesis was conducted in a Bayesian framework that involves updating prior beliefs based on the data available to reflect the current state of knowledge (144). This is achieved by placing prior distributions (commonly referred to as priors) on the parameters estimated. Study data included in the evidence synthesis is then used to update these priors jointly to provide the parameter estimates of interest. In our analysis, prior distributions were placed on the relative treatment effects, study-specific effects and random effects standard deviation (for random effects models).

Flat priors were chosen for the treatment and study specific terms (141). For the analysis conducted on the log odds scale, these were normally distributed with mean 0 and variance 10,000. For the random effects standard deviation, a uniform distribution of parameters 0 and 5 was chosen. This distribution assumes that any value between 0 and 5 is equally likely to represent the between-study variance in the treatment effects.

For the analysis conducted on the absolute risk scale, the study-specific term followed a uniform distribution of parameters 0 and 1 to ensure the baseline probability remained in the interval

[0,1]. Warn (2002) (145) describe a constraint which can be used in pairwise meta-analysis to also constrain $p_{i,k}$ to the interval [0,1]. However the constraint was not implemented in this analysis as the Adaptive Rejection Metropolis sampler used in JAGS (146) did not generate samples for the model parameters that led to the estimated probabilities for the individual study arms being outside the range of [0,1] The predicted probabilities of response for individual treatments based on a given reference probability of response and assuming consistency could potentially lie outside of the range 0 to 1 due to the linear link function.

4.10.6.5 Initial values

Initial values were specified for the parameters being estimated with prior distributions, namely treatment effects, study-specific effects and random effects standard deviation (for random effects models). These initial values were then updated for each simulation.

Two chains of initial values were run to assess whether the choice of initial value affected the posterior estimate. The initial values for these parameters were chosen by selecting random samples from a normal distribution for the log odds model and from a uniform distribution for the risk difference model (to ensure the initial values lay within [0,1]).

4.10.6.6 Simulations

The models were fitted using the JAGS software package version 4.2.0 (for risk differences) and OpenBUGS version 3.2.3 (for log odds). The corresponding code is presented in Appendix 9. The Markov chain Monte Carlo (MCMC) estimator was run for 100,000 burn-in simulations and monitored for a further 150,000 simulations.

Convergence and autocorrelation

Convergence within and between chains was assessed by examining trace plots. Convergence was assumed to be adequate if the parameter estimate range was consistent, and there was little deviation in the estimates as the number of simulations increased. The Rhat statistic is the square root of the ratio of between-chain and within-chain variability, and it represents the potential scale reduction factor. This statistic was investigated for all parameters estimated in the models.

Autocorrelation is a measure of the correlation between posterior simulations within a chain of a parameter. Where autocorrelation was high, the number of simulations was increased or chains thinned in an attempt to reduce this.

4.10.6.7 Model fit

The fit of the fixed and random effects models was compared using the deviance information criterion (DIC), which penalises the deviance by the effective number of parameters, as a measure of relative fit (141, 144). Lower DIC is indicative of improved fit. Where marginal differences were observed between the models in terms of DIC, the model with improved convergence and autocorrelation was selected as the best fitting model. In circumstances where these were also similar, the random effects model was chosen to avoid the assumption of a common effect size across studies.

The best fitting model was identified for each analysis and reported in the results section (Section 4.10.7).

4.10.6.8 Inconsistency checking

A key assumption of NMA is that the direct and indirect evidence are estimating the same parameters, meaning the evidence is consistent. For example, the relative effect of treatment B versus C can be estimated directly from the BC trials or indirectly from the treatment effect of the AC trials minus the AB trials. Therefore, the treatment effect we infer from indirect evidence through the NMA is assumed to be the same as the direct trial evidence. Where this is not the case, this is referred to as inconsistency and can be assessed through a variety of analytical methods.

Inconsistency is the variation in treatment effects between pair-wise contrasts. This can be caused by treatment effect modifiers and where there is an imbalance in the distribution of treatment effect modifiers in direct and indirect evidence (147). When there is a closed 'loop' in the network (e.g. evidence to connect treatment A to B, B to C and A to C), the indirect evidence obtained from the NMA can be compared with the direct evidence to check for inconsistency.

A number of closed loops were identified in the network diagrams:

- In the GT1 treatment-naïve network, all loops were created by multi-arm trials which also shared at least one edge with at least one other trial providing the potential to assess inconsistency.
- In the GT3 treatment-naïve network one loop shared an edge with one other trial (SOF12+Peg-IFN+RBV vs SOF16+RBV16 vs SOF24+RBV24).

4.10.7 *NMA results*

Results have been presented as forest plots for each analysis. These present the risk difference estimated for the treatment comparisons alongside the 95% CrI.

Forest plots have been presented for each binary endpoint analysis which indicate the treatment effects for all treatments versus the reference treatment (Peg-IFN+RBV). These forest plots provide the treatment effects obtained for a common reference treatment that can indicatively provide a ranking of the treatment effects.

The ASTRAL-1 study was connected to the GT1 treatment-naïve network via its PBO12 arm (Figure 9). This arm had 0% SVR, as did the PBO12 arm of the Zeuzem 2004 study which connected ASTRAL-1 to the network. The log odds scale uses the transform: $\mathrm{logit}(p) = \log(\frac{p}{1-p})$, which has vertical asymptotes at $p = 0$ or $p = 1$; small changes in p near these boundaries can thus lead to very large changes in the log odds. With all information on PBO12 near the $p = 0$ boundary, use of the log odds scale resulted in very wide credible intervals.

In light of this, results on the risk difference scale were deemed to be a more appropriate method of generating relative efficacy estimates and are thus presented.

4.10.7.1 Base-case

The risk difference represents the difference in risks between arms where the risk of an event in the treatment arm is a/(a+b) and the control arm is c/(c+d)) (148). Specifically, the risk difference is given by the following:

$$RD = \frac{a}{a+b} - \frac{c}{c+d}.$$

Negative values of the risk difference represent a reduction in risk and vice versa, for the treatment arm relative to the control arm.

In this analysis, results on the absolute risk difference scale present treatment effects as median difference in probability of SVR compared to the reference treatment. A risk difference less than zero therefore represents a decreased probability of achieving SVR for each treatment compared to Peg-IFN+RBV, and conversely, a risk difference greater than zero represents an increased probability of achieving SVR for each treatment compared to Peg-IFN+RBV.

A significant risk difference can be inferred from the credible intervals; intervals above or below zero indicate a significant risk difference in favour or against the treatment arm respectively, compared to the reference treatment. Where the interval crosses zero, it can be inferred that there is no evidence of a significant difference in risk between the treatment arm and the reference treatment.

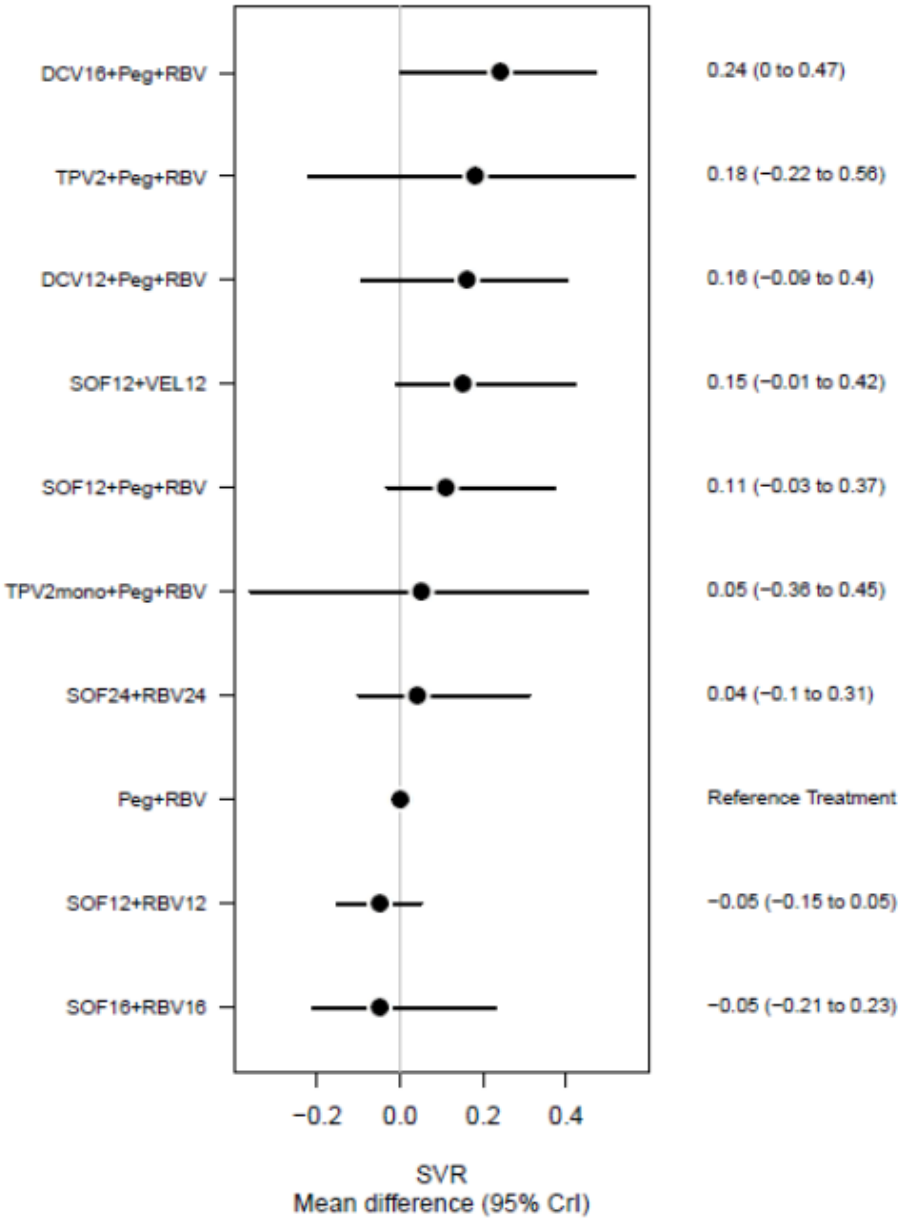
GT3 treatment naïve

Results are presented as a forest plot for all treatment compared with Peg-IFN+RBV in Figure 10. Fixed and random effects models were run with a thinning factor of 20. Convergence and autocorrelation were assessed and were acceptable for the fixed effects model. Although the two models had similar DIC (DIC=90.97 for fixed effects, DIC=91.57 for random effects), the fixed effects model was chosen as it had better convergence and autocorrelation.

There was no evidence for a statistically significant difference in risk of SVR compared to Peg-IFN+RBV for any of the treatments in the GT3 treatment-naïve network.

SOF12+RBV12 and SOF16+RBV16 showed decreases in SVR compared to Peg-IFN+RBV while all other treatments showed increases. For DCV16+Peg-IFN+RBV and to a lesser extent for SOF12+VEL12, the positive difference in risk of SVR was on the borderline of statistical significance.

Figure 10: Forest plot of risk differences for SVR fixed effects model (treatments vs. Peg-IFN+RBV) – GT3 treatment-naïve



BOC, boceprevir; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; PBO, placebo; Peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; VEL, velpatasvir.

GT1 treatment naïve

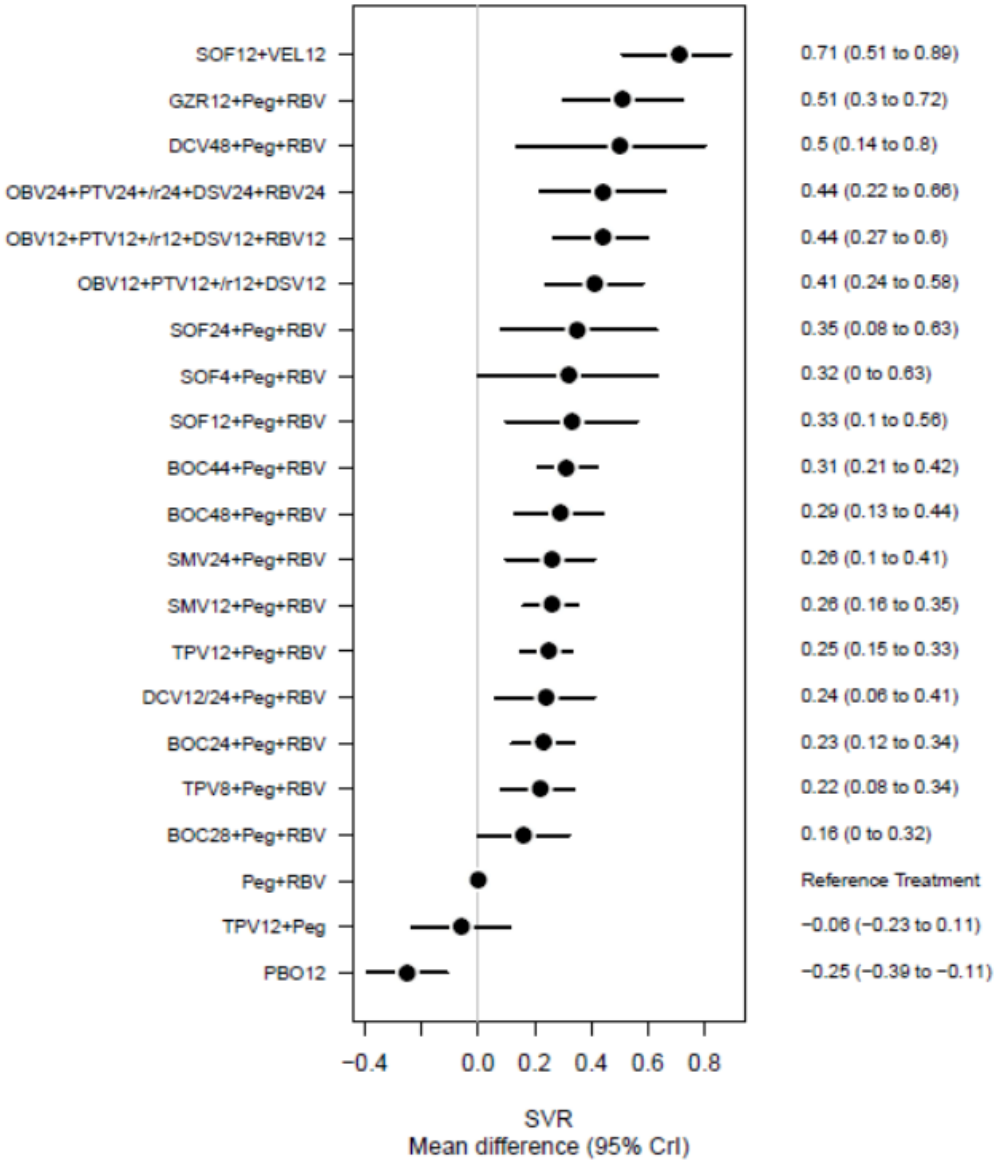
Results are presented as a forest plot for all treatments compared with Peg-IFN+RBV in Figure 11. Fixed and random effects models were run with a thinning factor of 20. Convergence and autocorrelation were assessed and were acceptable. Although the two models had similar DIC (DIC=364.68 for fixed effects, DIC=366.71 for random effects), the random effects model was chosen to avoid the assumption of a common effect size across studies.

Nearly all treatments showed a statistically significant increase or decrease in risk compared to Peg-IFN+RBV. PBO12 had a statistically significant negative risk difference (decrease in risk of

SVR) compared to Peg-IFN+RBV, while TVR12+Peg-IFN showed a decrease in risk which was not statistically significant. SOF24+Peg-IFN+RBV and BOC28+Peg-IFN+RBV showed borderline significant increases in risk of SVR.

All other treatments had statistically significant increases in risk of SVR compared to the reference treatment. In particular, SOF12+VEL12 demonstrated significant evidence of a positive risk difference compared to Peg-IFN+RBV.

Figure 11: Forest plot of risk differences for SVR random effects model (treatments vs. Peg-IFN+RBV) – GT1 treatment-naïve



BOC, boceprevir; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; PBO, placebo; Peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; VEL, velpatasvir.

4.10.7.2 Sensitivity analysis: Unpooled Peg-IFN+RBV duration

A sensitivity analysis was run in which the durations of Peg-IFN+RBV treatment (with or without additional therapies) were not pooled. Generally the effect of unpooling Peg-IFN-IFN+RBV data had little effect on the direction of effect observed in the base-case analysis. Further details are

provided in Appendix 10. It should be noted that this assumption had little impact in GT3 treatment-naïve populations, where all studies utilising Peg-IFN+RBV as a treatment arm used 24 weeks of treatment.

4.10.8 *NMA discussion*

A systematic literature review and NMA was undertaken to explore the feasibility of obtaining comparative data for SOF/VEL versus all relevant comparators across CHC of different genotypes.

In this NMA, only the evidence networks for GT1 treatment-naïve and GT3 treatment-naïve were analysed, with meaningful analyses in other populations being limited by data availability.

For the purposes of populating the economic model for SOF/VEL the NMA was limited in two key areas:

- An NMA network could not be formed for all the populations of interest (i.e. treatment-naïve patients with GT2/4/5/6 infection and treatment-experienced patients with GT1/2/3/4/5/6 infection)
- For patient populations where an NMA was feasible (GT1 treatment-naïve and GT3 treatment-naïve), these analyses had several limitations:
    - The structure of the economic model required that efficacy data were split by cirrhotic (METAVIR F4) and non-cirrhotic (METAVIR F0-F3) status. It was not possible to carry out analyses by fibrosis stage in the NMA due to the number of disconnections in each population
    - The NMA could not provide specific estimates for the GT1 sub genotypes a and b, which are important given that OBV/PTV/RTV+DSV is recommended for different durations in cirrhotic patients depending on GT1 sub genotype
    - The following treatments that fall within the NICE decision problem were disconnected from the NMA network and therefore efficacy data from individual studies would have to be used. The inconsistency between the efficacy data sources would cause difficulty in interpreting pairwise comparisons and most importantly require multiple probabilistic sensitivity analyses
        - GT1 treatment-naïve: LDV/SOF 8 weeks; LDV/SOF 12 weeks; LDV/SOF 24 weeks; LDV/SOF+RBV 12 weeks; SOF+DCV 12 weeks
    - The NMA presented risk differences in the base-case analysis. The risk difference is naturally constrained, which may create difficulties when applying results to patient groups that are different from those observed in the studies. For example, the NMA estimated a risk difference of 0.71 (95% CrI: 0.51, 0.89) for SOF/VEL 12 weeks relative to Peg-IFN+RBV 48 weeks in the GT1 treatment-naïve population. In the treatment-naïve non-cirrhotic population in the economic model, the SVR rate for Peg-IFN+RBV 48 weeks is 43.6%, leading to an impossible estimated SVR rate of 114.6% for SOF/VEL 12 weeks
    - As described previously, when the extracted disease and patient baseline characteristics of the studies informing the GT3 treatment-naïve network were reviewed, the studies appeared to be generally homogeneous with the exception for

METAVIR score. This is a known significant treatment effect modifier in hepatitis C (14). However, very importantly and as described in detail below, and in Section 5.3.3, it was obvious that the reported results of one small Phase II trial (ELECTRON) lacked clinical face validity and were implausible. Given that the inclusion of this small Phase II dataset was necessary in order to construct the GT3 treatment-naive network, the indirect treatment effect estimates reported in the GT3 treatment-naive analysis were misleading.

- The studies which inform the GT3 treatment-naïve network were homogeneous in terms of baseline characteristics, except for METAVIR score. This is a known treatment effect modifier in hepatitis C (14).
  - In the AI444-031 study (80), 15% of GT3 patients in the DCV16+Peg-IFN+RBV arm were cirrhotic. The proportions of cirrhotic patients in the studies which connect SOF12+VEL12 to the reference treatment, Peg-IFN+RBV, varied between 16–38% (ASTRAL-3, BOSON, Chulanov AASLD 2014, FISSION), with one study (ELECTRON) having no patients with cirrhosis. Therefore the proportion of patients who were cirrhotic was higher in the majority of studies compared with the AI444-031 study.
  - Moreover, the ELECTRON study included only 6 or 7 patients in the relevant treatment arms.
  - Ideally, this heterogeneity would be adjusted for through meta-regression or subgroup analysis. However, meta-regression was not feasible due to inconsistency in reporting of METAVIR score across studies. Specifically, studies which evaluated a mixed population in terms of genotype typically reported baseline characteristics for the whole population, or GT2 and GT3 combined. Subgroup analyses were also not feasible due to the number of disconnections in the network. As such, the impact of heterogeneity in METAVIR score across studies on the estimated relative treatment effects (in terms of SVR) is unknown and hence the strong likelihood is that this would introduce bias.

Overall, the NMA does not provide relative treatment effects by treatment history, sub genotype and fibrosis stage. As such, the results from the NMA could not be considered appropriate for the economic model, in which analyses comparing SOF/VEL to the comparators listed in the NICE scope stratified according to patient treatment history and cirrhosis status are required. It was therefore considered more robust to populate the economic model with efficacy data from individual studies in all patient groups. This allowed the economic model to be populated with efficacy data that was stratified by treatment history and cirrhosis status where the available data allowed, an approach which was felt to be more transparent and in line with the requirements of the NICE scope.

GT3 treatment-naïve analysis

The systematic literature review underpinning the NMA has shown that in order to construct a network of evidence in the GT3 treatment-naïve population using randomised trials, it is necessary to use the Phase II ELECTRON trial, 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% (30).

The finding of an SVR of 100% with SOF+RBV 12 weeks in GT3 treatment-naïve patients 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 GT3 treatment-naive patients was 56% (19). 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 described in Section 5.3.3.

Data from the Phase III VALENCE trial should also be considered. VALENCE was initially designed to compare SOF+RBV 12 weeks with placebo in patients with HCV GT2 or GT3 infection. However, emerging data from the Phase III FUSION trial indicated that patients with HCV GT3 infection had higher response rates when treated for 16 weeks compared with 12 weeks. As a result the VALENCE trial was unblinded, and treatment for all patients with HCV GT3 infection was extended to 24 weeks and the placebo group terminated. The trial was redefined as a descriptive study to characterise SVR rates in patients with HCV GT2 infection treated for 12 weeks, and in patients with HCV GT3 infection treated for 24 weeks, with no plans for hypothesis testing (for this reason, the VALENCE trial did not fulfil the criteria for inclusion in the systematic literature review described in Section 4.1). Prior to study unblinding, 11 patients with HCV GT3 infection received treatment with SOF+RBV 12 weeks; 2 patients were treatment-naïve (149). It is therefore difficult to make a robust inference regarding the likely treatment effect that would have been seen in the GT3 treatment-naïve population treated with SOF+RBV 12 weeks if the trial had continued as planned. The SVR rate in the entire cohort of patients who received SOF+RBV 12 weeks was 27% (3/11) (149).

In the Phase III FUSION and POSITRON trials, the SVR rates for SOF+RBV 12 weeks were 29.7% (19/64) and 61.2% (60/98), respectively (31). While the patients included in these trials were treatment-experienced rather than treatment-naïve, these data serve to illustrate that an SVR rate for SOF+RBV 12 weeks of 100% in GT3 treatment-naïve patients lacks clinical credibility. SOF+RBV 12 weeks has not received regulatory approval for the treatment of GT3 patients.

ELECTRON was a small Phase II study conducted at two centres in New Zealand, which was designed as an initial four-cohort dose ranging study to assess safety and tolerability of SOF±RBV±Peg-IFN alfa-2a, involving a small number of patients in each trial arm, all of whom were non-cirrhotic. The initial 40 treatment naïve patients with HCV GT2 or GT3 infection (25 of the 40) were randomly allocated to one of four groups, all receiving 12 weeks SOF+RBV with three groups also receiving 4, 8 or 12 weeks of Peg-IFN. In GT3 specifically, 6 patients received 12 weeks SOF+RBV alone, with 6, 6 and 7 receiving in addition 4, 8 or 12 weeks Peg-IFN, respectively. All patients achieved SVR24, irrespective of whether they received interferon or not. On the basis of these results, the study was subsequently amended to include several additional arms, in one of which 12 weeks SOF was given as monotherapy to GT2 and GT3 treatment-naïve patients, resulting in SVR in 60% (6/10) (30).

The ELECTRON trial results did not differentiate between SOF+Peg-IFN+RBV 12 weeks and SOF+RBV 12 weeks in terms of efficacy in GT3 treatment-naïve patients. This is likely to be responsible for the misleading overall effect estimates within the NMA network. For example, the treatment effect of SOF/VEL 12 weeks versus Peg-IFN+RBV 24 weeks in GT3 treatment-naïve patients in the NMA was found to be 0.15 (95% CrI: -0.01, –0.42). This result appears spuriously compressed and potentially lacks clinical face validity. For this reason, external

clinical expert opinion was sought regarding the results of the NMA in an attempt to appropriately interpret the findings and explore the robustness of the results for use in the economic model (see Section 5.3.3 [clinical validation]).

To explore the impact of the ELECTRON trial data on the GT3 treatment-naïve network, a sensitivity analysis was undertaken by relaxing the requirement to analyse trial data stratified by treatment history. This enabled usage of the Phase III FUSION trial of SOF+RBV 12 weeks versus SOF+RBV 16 weeks in GT3 treatment-experienced patients, and avoided the necessity of using data from the ELECTRON trial. The resulting network diagram is provided in Appendix 10.

The efficacy of SOF+RBV 12 weeks in GT3 patients in this network (SVR rates: treatment-naïve in FISSION of 56% (19); treatment-experienced in FUSION of 31.3% (31)) is more in line with clinical expectation compared with the corresponding result of 100% SVR for SOF+RBV in the ELECTRON trial. For the comparison of SOF/VEL 12 weeks versus Peg-IFN+RBV 24 weeks, the treatment effect obtained in this sensitivity analysis was 0.30 (95% CrI: 0.03, 0.58). This treatment effect can be considered to have greater clinical validity than the treatment effect of 0.15 obtained from the original NMA network. Implementation of this treatment effect using SOF/VEL 12 weeks as a reference treatment (assuming an SVR rate with SOF/VEL 12 weeks of 97.1% in GT3 treatment-naïve patients from the ASTRAL-3 trial) would imply an SVR rate of 67.1% with Peg-IFN+RBV. Interestingly, this SVR rate is similar to that reported in Section 3.7 from a real-world effectiveness study recently conducted in a large UK HCV treatment centre (20). In that study, it was found that the efficacy of Peg-IFN+RBV in GT3 patients in the intention-to-treat population was 60.5%, while the SVR rate in the per-protocol population was 68.8%.

In addition, and as outlined in Section 4.10.3, the trials included in the GT1 treatment-naïve and GT3 treatment-naïve networks inconsistently reported the proportion of included patients who were cirrhotic. When considering the trials that did report this information, it is clear that the proportion of cirrhotic patients varied significantly. As discussed in Section 5.3.3 (clinical validation), external clinical expert opinion was obtained regarding the potential heterogeneity that would result in a network in which the constituent trials contained varying proportions of cirrhotic patients. 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 versus Peg-IFN+RBV. Clinical expert opinion was the heterogeneity would particularly affect Peg-IFN+RBV treatment, which is known to perform quite differently in non-cirrhotic, compared with cirrhotic patients (see Section 5.3.3).

In summary, given the requirement to include results from the ELECTRON trial, and the heterogeneity introduced in the network from pooling data from cirrhotic and non-cirrhotic patients, the clinical experts agreed that an approach of using the results of the NMA directly in the economic model was unlikely to be robust. This is particularly true 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.

In terms of the comparison of SOF/VEL 12 weeks versus Peg-IFN+RBV 24 weeks in GT3 treatment-naïve patients without cirrhosis, the relevant trial-level SVR rates used in the economic model are 98.1% and 71.2% from the ASTRAL-3 and FISSION trials, respectively. While greater than the treatment effect estimate from the original NMA (0.15), this treatment effect estimate of 26.9% appears conservative in the context of the NMA sensitivity analysis outlined above, which suggests that the true treatment effect may be up to 30%. In addition, the model assumption regarding the efficacy of Peg-IFN+RBV 24 weeks (71.2%) also appears conservative, given the likely real-world effectiveness of Peg-IFN+RBV 24 weeks, [redacted], as observed in the UK NHS setting (20).

GT3 treatment-experienced

As shown in Table 35, a small network connecting SOF/VEL 12 weeks to SOF+Peg+RBV 12 weeks via SOF+RBV 24 weeks was possible. However, this was not explored further. Consistent with the overall approach taken to the economic modelling described in Section 4.10.9, SVR rates from individual trials were considered more appropriate for these model comparisons. For SOF+Peg+RBV 12 weeks, the relevant data came from the Phase III BOSON trial, which is a large randomised study in which SVR rates were stratified by treatment history and cirrhosis status, which enabled the SVR rates for this treatment to be included in the economic model in line with the NICE scope.

4.10.9 *Naïve comparison*

As described in Section 4.10.8, the clinical data to inform the economic modelling were derived from naïve comparisons. Comparisons were based on studies identified by the systematic review (described in Section 4.2). Data were supplemented with non-randomised data highlighted in product SmPCs or available from conference proceedings (EASL). Studies are listed in Table 39 for each intervention of relevance to the NICE decision problem (i.e. regimens recommended by NICE stratified by genotype, treatment-experience and cirrhotic status). Details of study design and justification for selection of each study are also provided. Patient characteristics are provided in Table 40. Outcomes data used in the economic model are provided in Section 5.6. Study design and patient baseline characteristics in the sets of trials used to provide SVR rates for the economic model (stratified by treatment history and cirrhosis status) are homogeneous, which further justifies the adoption of this approach.

In GT2 treatment-naïve patients the relevant comparators are SOF/VEL 12 weeks, SOF+RBV 12 weeks and Peg-IFN+RBV 24 weeks. The availability of data from ASTRAL-2 for SOF/VEL versus SOF+RBV and from FISSION for SOF+RBV versus Peg-IFN+RBV allowed an adjusted indirect comparison of SOF/VEL versus Peg-IFN+RBV to be performed, using SOF+RBV as the common comparator. This is described further in Section 4.10.9.1.

As described and justified in detail in Section 4.10.8, the results of the NMA were not considered robust or credible for use in the economic model. In the GT3 treatment-naïve network, given the requirement to include results from the ELECTRON trial, and the heterogeneity introduced in the network from pooling data from cirrhotic and non-cirrhotic patients, using the results of the NMA directly in the economic model would not be robust and therefore naïve comparisons using SVR rates from the most appropriate individual trials was more appropriate. This is particularly justifiable in the context of the NICE scope, which requires economic model analyses to be stratified by treatment history and cirrhosis status, for each genotype.

Table 39: Study design for all relevant studies used in base-case economic evaluation

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
GT3 TN (NC and CC)									
SOF/VEL 12w	ASTRAL-3 (Section 4.3)	3	Randomised, multicentre, active controlled	Open-label	HCV GT3, plasma HCV RNA≥10^4 IU/mL at screening	TN/TE	NC/CC (30% CC)	HCV RNA <LLOQ, 12 weeks after EOT LLOQ=15 IU/mL	NA
SOF+RBV 24w	ASTRAL-3 (Section 4.3)		As above						BOSON, VALENCE, ELECTRON; ASTRAL-3 is the largest Phase III dataset for SOF+RBV in GT3 patients and allows a head to head comparison to be made with SOF/VEL. As such, it is a more appropriate source than the BOSON, VALENCE or ELECTRON trials
SOF+Peg-IFN+RBV 12w	BOSON (Foster 2015 (86))	3	Randomised	Open-label	HCV GT2/3, HCV RNA ≥10^4 IU/mL at screening	TN/TE	NC/CC (37% CC)	HCV RNA <LLOQ, 12 weeks after EOT LLOQ=15 IU/mL	ELECTRON, PROTON, LONESTAR-2: The BOSON trial data were considered more appropriate due to the larger size of this dataset, the fact that it was a Phase III randomised trial and that it reported SVR rates for SOF+Peg-IFN+RBV 12w in each GT3 patient population included in the NICE scope

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
SOF+DCV 12wk (F3-F4 NC)	ALLY-3 (Nelson 2015 (150))	3	Non-randomised, two cohort	Open-label	HCV GT3, HCV RNA $>10^4$ IU/mL at screening	TN/TE	NC/CC (21% CC)	HCV RNA <LLOQ, 12 weeks after EOT LLOQ=25 IU/mL	AI444040; ALLY-3 is a large dataset and provides data for SOF+DCV 12w in patients with F3/F4 liver histology. In addition, this study was used by BMS in support of GT3 TN F3/F4 patients in TA364 (56). As such, it is a more appropriate source than the AI444040 trial
SOF+DCV+RBV 24wk (CC)	No data: use ALLY-3 (Nelson 2015 (150)) data for SOF+DCV 12wk in CC	See above							NA
Peg-IFN+RBV 24w	FISSION (SmPC and Lawitz et al, 2013 (19, 24))	3	Randomised, multi-centre, active controlled	Open-label	HCV GT2/3, plasma HCV RNA $>10^4$ IU/mL at screening	TN	NC/CC (20% CC)	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ=25 IU/mL	FISSION is a large Phase III trial dataset and allows treatment outcomes for Peg-IFN + RBV to be stratified by prior treatment history and cirrhosis status, in line with the NICE scope
GT3 TE (NC and CC)									
SOF/VEL 12w	ASTRAL-3 (Section 4.3)	See GT3 TN							NA

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
SOF+RBV 24w	ASTRAL-3 (Section 4.3)	See GT3 TN							VALENCE; The ASTRAL-3 trial is the largest Phase III dataset for SOF+RBV in GT3 patients and allows a head to head comparison to be made with SOF/VEL. As such it is more appropriate than the VALENCE trial
SOF+Peg-IFN+RBV 12w	BOSON (Foster 2015 (86))	See GT3 TN							LONESTAR-2; The BOSON trial data were considered more appropriate due to the larger size of this dataset, the fact that it was a Phase III randomised trial and that it reported SVR rates for SOF+Peg-IFN+RBV 12w in each GT3 patient population included in the NICE scope
SOF+DCV 12wk (F3-F4 NC)	ALLY-3 (Nelson 2015 (150))	See GT3 TN							NA
SOF+DCV+RBV 24wk (CC)	No data: use ALLY-3 (Nelson 2015 (150)) data for SOF+DCV 12wk in CC	See GT3 TN							NA
Peg-IFN+RBV 24w	Lagging 2013 (151)	3	Non-randomised, multicentre	Open-label	HCV GT2/3, HCV RNA >15 IU/mL	TE (prior relapse)	Compensated cirrhosis included	24 weeks after EOT LLOD=15 IU/ml	Accepted previously in NICE TA330 for SOF. Derivation of SVR rates provided in Appendix 11

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
	Shoeb 2011 (152)	NA	Retrospective cohort	NA	HCV GT3	TN	NC/CC (24% CC)	Absence of detectable HCV RNA 24 weeks after EOT	Accepted previously in NICE TA330 for SOF. Derivation of SVR rates provided in Appendix 11
GT1 TN (NC and CC)									
SOF/VEL 12w	ASTRAL-1 (Section 4.3)	3	Randomised, multicentre, placebo controlled	Double-blind	HCV GT1–6, plasma HCV RNA≥10^4 IU/mL at screening	TN/TE	NC/CC (19% CC)	HCV RNA <LLOQ, 12 weeks after EOT LLOQ=15 IU/mL	NA
LDV/SOF 8w (NC)	ION-3 (SmPC and Kowdley 2014 (21, 27)	3	Randomised, multicentre	Open-label	HCV GT1 HCV RNA≥10^4 IU/mL at screening	TN	NC	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ=25 IU/mL	NA
LDV/SOF 12w (CC)	ION-1 (SmPC and Afdhal 2014 (21, 101)	3	Randomised, multicentre	Open-label	HCV GT1 HCV RNA≥10^4 IU/mL at screening	TN	NC/CC (16% CC)	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ=25 IU/mL	NA
OBV/PTV/RTV+DSV 12w (GT1b NC)	PEARL-III (Ferenci 2014 (112))	3	Randomised, multicentre, placebo-controlled trial	Double-blind RBV, open-label PTV-450+RTV+OBV+DSV	HCV GT1b HCV RNA≥10^4 IU/mL at screening	TN	NC	HCV RNA <LLOQ, 12 weeks after EOT LLOQ=25 IU/mL	NA

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
OBV/PTV/RTV+DSV+RBV 12w (GT1a NC)	PEARL-IV (Ferenci 2014 (112))	3	Randomised, multicentre, placebo-controlled trial	Double-blind RBV, open-label PTV-450+RTV+OBV+DSV	HCV GT1a HCV RNA≥10^4 IU/mL at screening	TN	NC	HCV RNA <LLOQ, 12 weeks after EOT LLOQ=25 IU/mL	SAPPHIRE-1: Comparable studies, which both included UK patients. SVR rates were almost identical in both trials.
OBV/PTV/RTV+DSV+RBV 12w (GT1b TN CC)	TURQUOISE-II (Poordad 2014 (137))	3	Randomised, multicentre	Open-label	HCV GT1 HCV RNA≥10^4 IU/mL at screening	TN/TE	CC	HCV RNA <LLOQ, 12 weeks after EOT LLOQ=25 IU/mL	NA
OBV/PTV/RTV+DSV+RBV 24w (GT1a TN CC)	TURQUOISE-II (Poordad 2014 (137))	See above							NA
SOF+Peg-IFN+RBV 12w	NEUTRINO (SmPC and Lawitz 2013 (19, 24))	3	Single arm	Open-label	HCV GT1/4/5/6, plasma HCV RNA >10^4 IU/mL at screening	TN	NC/CC (17% CC)	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ=25 IU/mL	NA
SOF+DCV 12w (F3-F4 NC)	AI444040 (Sulkowski 2014 (81))	2	Multicentre parallel randomised	Open-label	HCV GT1/2/3 HCV RNA≥10^4 IU/mL at screening	TN/TE	NC	HCV RNA <LLOQ, 12 weeks after EOT LLOQ=25 IU/mL	NA
SOF+DCV+RBV 24wk (CC)	ANRS CO22 HEPATHER (Pol 2015 EASL) (153)	NA	French multicentre observational cohort study	Open-label	HCV GT1	TN/TE	NC/CC (78% CC)	SVR4	NA

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
SMV+Peg-IFN+RBV RGT	QUEST 1 (C208) (SmPC and Jacobsen 2014 (26, 120))	3	Randomised, multicentre, placebo-controlled	Double-blind	HCV GT1 HCV RNA≥10^4 IU/mL at screening	TN	NC/CC (12% METAVIR F4)	HCV RNA concentration of <25 IU/mL undetectable at EOT and <25 IU/mL detectable or undetectable 12 weeks after the planned EOT	NA
	QUEST 2 (C216) (SmPC and Manns 2014 (26, 121))	3	Randomised, multicentre, placebo-controlled	Double-blind	HCV GT1 HCV RNA≥10^4 IU/mL at screening	TN	NC/CC: Cirrhosis allowed if ultrasound ≤6 months showed no signs of HCC. Decompensated cirrhosis excluded	HCV RNA concentration of <25 IU/mL undetectable at EOT and <25 IU/mL detectable or undetectable 12 weeks after the planned EOT	NA
Peg-IFN+RBV 48w	IDEAL (McHutchison et al, 2009 (154))	NR	Randomised, multicentre	Double-blinded	Detectable plasma HCV RNA level and chronic HCV GT1 infection	TN	Compensated liver disease	Undetectable HCV RNA 24 weeks after EOT LLOD: 27 IU/ml	McHutchison is a large dataset and allows treatment outcomes on Peg-IFN in GT1 TN patients to be stratified by cirrhosis status
GT1 TE (NC and CC)									
SOF/VEL 12w	ASTRAL-1 (Section 4.3)	See GT1 TN							NA

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
LDV/SOF 12w	ION-2 (SmPC and Afdhal 2014 (21, 102))	3	Randomised, multicentre	Open-label	HCV GT1 HCV RNA≥10^4 IU/mL at screening	TE	NC/CC (20% CC)	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ=25 IU/mL	NA
OBV/PTV/RTV+DSV 12w (GT1b NC)	PEARL-II (Andreone 2014 (111))	3	Randomised, multicentre	Open-label	HCV GT1b HCV RNA≥10^4 IU/mL at screening	TE	NC	HCV RNA <25 IU/mL, 12 weeks after EOT	NA
OBV/PTV/RTV+DSV+RBV 12w (GT1a NC)	SAPPHIRE-II (Zeuzem 2014 (126))	3	Randomised, multicentre, placebo-controlled	Double-blinded	HCV GT1 HCV RNA≥10^4 IU/mL at screening	TE	NC	HCV RNA <25 IU/mL, 12 weeks after EOT	NA
OBV/PTV/RTV+DSV+RBV 12w (GT1b TE CC)	TURQUOISE-II (Poordad 2014 (137))	See GT1 TN							NA
OBV/PTV/RTV+DSV+RBV 24w (GT1a TE CC)	TURQUOISE-II (Poordad 2014 (137))	See GT1 TN							NA
SOF+Peg-IFN-RBV 12w	No study available. SVRs taken from FDA bridging analysis								NA
SOF+DCV 12w (F3-F4 NC)	AI444040 (Sulkowski 2014 (81))	See GT1 TN							NA
SOF+DCV+RBV 24wk (CC)	ANRS CO22 HEPATHER (Pol 2015 EASL) (153)	See GT1 TN							NA

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
SMV+Peg-IFN+RBV RGT	PROMISE (HPC3007) (SmPC and Forns 2014 (26, 115))	3	Randomised, multicentre, placebo-controlled	Double-blind	HCV GT1 HCV RNA≥10^4 IU/mL at screening	TE	NC/CC (15% CC)	HCV RNA <25 IU/mL undetectable at actual EOT and HCV RNA<25 IU/mL 12 weeks after EOT	NA
Peg-IFN+RBV 48w	REALIZE (Study C216) (TVR SmPC and Zeuzem 2011 (32, 122))	3	Randomised, multicentre, placebo-controlled	Double-blind	HCV GT1. Detectable HCV RNA	TE	NC/CC (26% CC)	Undetectable HCV RNA 24 weeks after EOT LLOD=10 IU/mL	REALIZE trial allows stratification of treatment outcomes on Peg-IFN+RBV in GT1 TE patients by cirrhosis status
GT2 TN (NC and CC)									
SOF/VEL 12w	ASTRAL-2 (Section 4.3)	3	Randomised, multicentre, active controlled	Open-label	HCV GT3, plasma HCV RNA ≥10^4 IU/mL at screening	TN/TE	NC/CC (14% CC)	HCV RNA <LLOQ, 12 weeks after EOT LLOQ=15 IU/mL	ASTRAL-1; ASTRAL-2 provides head-to-head data vs SOF+RBV and enables an adjusted indirect comparison of SOF/VEL 12w versus Peg-IFN+RBV 24w using the Bucher method, using SOF+RBV 12w as a common comparator
SOF+RBV 12w	ASTRAL-2 (Section 4.3)	As above							FISSION, ELECTRON (NC); FUSION, POSITRON, VALENCE (CC); ASTRAL-2 is the largest dataset and provides head-to-head comparison with SOF/VEL

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
Peg-IFN+RBV 24w	FISSION (SmPC and Lawitz et al, 2013 (19, 24)) Informs Bucher indirect comparison with SOF/VEL (See Section 4.10.9.1)		See GT3 TN						FISSION is a large and recent dataset. Using FISSION allows treatment outcomes for Peg-IFN+RBV to be stratified by prior treatment history and cirrhosis status. Using the FISSION data also enables an adjusted indirect comparison of SOF/VEL 12w versus Peg-IFN+24w using the Bucher method, using SOF+RBV 12w as a common comparator
GT2 TE (NC and CC)									
SOF/VEL 12w	ASTRAL-2 (Section 4.3)		See GT2 TN						ASTRAL-2 provides head-to-head data vs SOF+RBV
SOF+RBV 12w	ASTRAL-2 (Section 4.3)		See GT2 TN						FUSION, VALENCE (NC & CC); ASTRAL-2 largest dataset and provides head-to-head comparison with SOF/VEL
Peg-IFN+RBV 24w	Lagging 2013/Shoeb 2011		See GT3 TE						Accepted previously in NICE TA330 for SOF. Derivation of SVR rates provided in Appendix 11
GT4/5/6 TN (NC and CC)									
SOF/VEL 12w	ASTRAL-1 (Section 4.3)		See GT1 TN						NA

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
LDV/SOF 12w	Study 1119 (SmPC and Abergel 2015 (155)) (GT4/5)	2	Single arm	Open-label	HCV GT4/5	TN/TE	NC/CC (22% CC)	SVR 12 weeks after EOT	NA
	Gane 2015 (98) (GT6)	2	Randomised (GT3 only), two centre	Open-label	HCV GT3 or 6, plasma HCV RNA ≥10^4 IU/mL at screening	TN/TE	NC/CC (27% CC)	HCV RNA ≤15 IU/mL 12 weeks after EOT	NA
OBV/PTV/RTV+RBV 12w	PEARL-I (Hezode 2015 (110))	2b	Randomised, multicentre	Open-label	HCV GT4, plasma HCV RNA >10^4 IU/mL at screening	TN/TE	NC	HCV RNA <25 IU/mL 12 weeks after EOT	NA
OBV/PTV/RTV+RBV 24w	No data								NA
SOF+Peg-IFN+RBV 12w	NEUTRINO	See GT1 TN							NA
SMV+Peg-IFN+RBV RGT	RESTORE (HPC3011) (Moreno 2015 (156))	3	Single arm, multicentre	Open-label	HCV GT4, plasma HCV RNA >10^4 IU/mL at screening	TN/TE	NC/CC (29% CC)	HCV RNA <25 IU/ml undetectable at actual EOT and HCV RNA <25 IU/ml undetectable or detectable 12 weeks after planned EOT.	NA
DCV+Peg-IFN+RBV 24w	COMMAND-4 (AI444042) (Hezode, 2015 (90))	3	Randomised, multicentre, placebo-controlled	Double-blinded	HCV GT4, plasma HCV RNA >10^4 IU/mL at screening	TN	NC/CC (10.5% CC)	HCV RNA <LLOQ at 12 weeks after EOT. LLOQ=25 IU/mL	NA

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
Peg-IFN+RBV 48w	COMMAND-4 (AI444042) (Hezode, 2015 (90))		As above						NA
GT4/5/6 TE (NC and CC)									
SOF/VEL 12w	ASTRAL-1 (Section 4.3)		See GT1 TN						NA
LDV/SOF 12w	Study 1119 (SmPC and Abergel 2015 (155)) (GT4/5)		See GT4/5/6 TN						NA
	Gane 2015 (98) (GT6)		See GT4/5/6 TN						NA
OBV/PTV/RTV+RBV 12w	PEARL-I (Hezode 2015 (110))		See GT4/5/6 TN						NA
OBV/PTV/RTV+RBV 24w	No data								NA
SOF+Peg-IFN+RBV 12w	Assumed equal to NEUTRINO (mainly GT4)		See GT1 TN						NA
SMV+Peg-IFN+RBV RGT	RESTORE (HPC3011) (Moreno 2015 (156))		See GT4/5/6 TN						NA
DCV+Peg-IFN+RBV 24w	No data; assume same as COMMAND-4 for TN		See GT4/5/6 TN						NA

Regimen of interest to decision problem†	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition	Alternate studies; justification where alternate studies are available
Peg-IFN+RBV 48w	No data; assume same as COMMAND-4 for TN		See GT4/5/6 TN						NA
Any GT with decompensated cirrhosis (TN/TE)									
SOF/VEL+RBV 12w	ASTRAL-4 (Section 4.11.3)	3	Randomised, multicentre	Open-label	HCV GT1–6, plasma HCV RNA≥10^4 IU/mL at screening	TN/TE	Decompensated cirrhosis (CPT class B)	HCV RNA <LLOQ, 12 weeks after EOT LLOQ=15 IU/mL	NA
LDV/SOF+RBV 12w	SOLAR-1 (SmPC & Charlton 2015 (21, 128))	2	Randomised, multicentre	Open-label	HCV GT1 or 4.	TN/TE	One cohort had patients with advanced cirrhosis (CPT class B or C) but had not undergone liver transplantation, the other had patients who had undergone liver transplantation (NC or cirrhosis+CPT class A-C)	HCV RNA <15 IU/mL 12 weeks after EOT	SOLAR-2; Comparable study to SOLAR-1. SVR rates were almost identical in both trials.

BOC, boceprevir; CPT, Child-Pugh-Turcotte; DCV, daclatasvir; DSV, dasabuvir; EOT, end of treatment; GT, genotype; LDV, ledipasvir; LLOD, lower limit of detection; LLOQ, lower limit of quantitation; NR, not reported; OBV, ombitasvir; Peg-IFN2a/2b, pegylated interferon 2a/2b; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; TVR, telaprevir; VEL, velpatasvir.

† Where NICE recommendations restrict a regimen to a subgroup by fibrosis or cirrhotic status this is included in parentheses after the regimen name.

Table 40: Patient characteristics

Regimen of interest to decision problem[†]	Source	N	Age	Race		Viral load (RNA IU/mL)	Liver histology, %		TE, %	Genotype, %							
			Mean	White %	Black %	Mean (SD)	F0-3	F4/ C/ DCC		1	1a	1b	2	3	4	5	6
GT3 TN (NC and CC)																	
SOF/VEL 12w	ASTRAL-3 (Section 4.3)	277 (TN+TE)	49	90	1	6.2±0.72	NR	29 (C)	26	-	-	-	-	100	-	-	-
SOF+RBV 24w	ASTRAL-3 (Section 4.3)	275 (TN+TE)	50	87	<1	6.3±0.71	NR	30 (C)	26	-	-	-	-	100	-	-	-
SOF+Peg-IFN+RBV 12w	BOSON (Foster 2015 (86))	197 (TN+TE)	50	84	1	6.3±0.69	NR	38 (C)	52	-	-	-	8	92	-	-	-
SOF+DCV 12wk (F3-F4 NC)	ALLY-3 (Nelson 2015 (150))	101 (TN)	53	88	4	NR	75	22[‡] (F4)/19 (C)	0	-	-	-	-	100			
SOF+DCV+RBV 24wk (CC)	No data: use ALLY-3 (Nelson 2015 (150)) data for SOF+DCV 12wk in CC	See above															
Peg-IFN+RBV 24w	FISSION (SmPC and Lawitz et al, 2013 (19, 24))	243	48	87	2	6.0±0.8	NR	21 (C)		-	-	-	28	72	-	-	-
GT3 TE (NC and CC)																	
SOF/VEL 12w	ASTRAL-3 (Section 4.3)	See GT3 TN															
SOF+RBV 24w	ASTRAL-3 (Section 4.3)	See GT3 TN															
SOF+Peg-IFN+RBV 12w	BOSON (Foster 2015 (86))	See GT3 TN															
SOF+DCV 12wk (F3-F4 NC)	ALLY-3 (Nelson 2015 (150))	See GT3 TN															

Regimen of interest to decision problem[†]	Source	N	Age	Race		Viral load (RNA IU/mL)	Liver histology, %		TE, %	Genotype, %							
			Mean	White %	Black %	Mean (SD)	F0-3	F4/ C/ DCC		1	1a	1b	2	3	4	5	6
SOF+DCV+RBV 24wk (CC)	No data: use ALLY-3 (Nelson 2015 (150)) data for SOF+DCV 12wk in CC	See GT3 TN															
Peg-IFN+RBV 24w	Lagging 2013 (151)	12	46.6	100	0	5.73±0.86	NR	NR	NR	-	-	-	25	75	-	-	-
	Shoeb 2011 (152)	604	43 (median)	NR	NR	NR	NR	24 (C)	0	-	-	-	-	100	-	-	-
GT1 TN (NC and CC)																	
SOF/VEL 12w	ASTRAL-1 (Section 4.3)	624 (All GTs)	54	79	8	6.3±0.66	NR	19 (C)	32	53	34	19	17	-	19	6	7
LDV/SOF 8w (NC)	ION-3 (SmPC and Kowdley 2014 (21, 27)	215	53	76	21	6.5±0.8	73	0 (F4)/ 0 (C)	0	100	80	20	-	-	-	-	-
LDV/SOF 12w (CC)	ION-1 (SmPC and Afdhal 2014 (21, 101)	214	52	87	11	6.4±0.69	NR	16 (C)	0	98	67	31	-	-	-	-	-
OBV/PTV/RTV+DSV 12w (GT1b NC)	PEARL-III (Ferenci 2014 (112))	209	49.2	94.2	4.8	6.33±0.67	100	0 (F4)/ 0 (C)	0	100	-	100	-	-	-	-	-
OBV/PTV/RTV+DSV+ RBV 12w (GT1a NC)	PEARL-IV (Ferenci 2014 (112))	100	51.6	86	10	6.64±0.50	100	0 (F4)/ 0 (C)	0	100	100	-	-	-	-	-	-
OBV/PTV/RTV+DSV+ RBV 12w (GT1b TN CC)	TURQUOISE-II (Poordad 2014 (137))	208	57.1	95.7	2.9	6.41±0.62	NR	100 (C)	59	100	67.3	32.7	-	-	-	-	-
OBV/PTV/RTV+DSV+ RBV 24w (GT1a TN CC)	TURQUOISE-II (Poordad 2014 (137))	172	56.5	93.6	3.5	6.53±0.52	NR	100 (C)	57	100	70.3	29.7	-	-	-	-	-
SOF+Peg-IFN+RBV 12w	NEUTRINO (SmPC and Lawitz 2013 (19, 24))	327	52	79	17	6.4±0.7	NR	17 (C)	0	89	69	20	-	-	9	<1	2

Regimen of interest to decision problem[†]	Source	N	Age	Race		Viral load (RNA IU/mL)	Liver histology, %		TE, %	Genotype, %							
			Mean	White %	Black %	Mean (SD)	F0-3	F4/ C/ DCC		1	1a	1b	2	3	4	5	6
SOF+DCV 12w (F3-F4 NC)	AI444040 (Sulkowski 2014 (81))	41	55	80	12	6.2±0.5	85	15 (F4)/ 0 (C)	0	100	83	17	-	-	-	-	-
SOF+DCV+RBV 24wk (CC)	ANRS CO22 HEPATHER (Pol 2015 EASL) (153)	92 (12+24w)	58	NR	NR	6±0.7	NR	75 (C), 7% (DCC)	83	100	61	36	-	-	-	-	-
SMV+Peg-IFN+RBV RGT	QUEST 1 (C208) (SmPC and Jacobsen 2014 (26, 120))	264	48	86	10	NR	87	12 (F4)	0	100	56	44	-	-	-	-	-
	QUEST 2 (C216) (SmPC and Manns 2014 (26, 121))	257	46	92	6	NR	93	7 (F4)/ 7 (C)	0	100	41	58	-	-	-	-	-
Peg-IFN+RBV 48w	IDEAL (McHutchison et al, 2009 (154))	1,035	47.6	70.8	19.3	6.34±0.64	10.6 (F3 or F4)	10.6 (F3 or F4)	0	100	61.3	36.1	-	-	-	-	-
GT1 TE (NC and CC)																	
SOF/VEL 12w	ASTRAL-1 (Section 4.3)	See GT1 TN															
LDV/SOF 12w	ION-2 (SmPC and Afdhal 2014 (21, 102))	109	56	77	22	6.5±0.44	NR	20 (C)	100	100	79	21	-	-	-	-	-
OBV/PTV/RTV+DSV 12w (GT1b NC)	PEARL-II (Andreone 2014 (111))	95	54.2	90.5	6.3	6.48±0.53	100	0 (F4)/ 0 (C)	100	100	-	100	-	-	-	-	-
OBV/PTV/RTV+DSV+RBV 12w (GT1a NC)	SAPPHIRE-II (Zeuzem 2014 (126))	297	51.7	90.6	7.4	6.55	32 (F2 or F3)	0 (F4)/ 0 (C)	100	100	58.2	41.4	-	-	-	-	-
OBV/PTV/RTV+DSV+RBV 12w (GT1b TN CC)	TURQUOISE-II (Poordad 2014 (137))	See GT1 TN															

Regimen of interest to decision problem[†]	Source	N	Age	Race		Viral load (RNA IU/mL)	Liver histology, %		TE, %	Genotype, %							
			Mean	White %	Black %	Mean (SD)	F0-3	F4/ C/ DCC		1	1a	1b	2	3	4	5	6
OBV/PTV/RTV+DSV+ RBV 24w (GT1a TN CC)	TURQUOISE-II (Poordad 2014 (137))	See GT1 TN															
SOF+Peg-IFN-RBV 12w	No study available. SVRs taken from FDA bridging analysis																
SOF+DCV 12w (F3-F4 NC)	AI444040 (Sulkowski 2014 (81))	See GT1 TN															
SOF+DCV+RBV 24wk (CC)	ANRS CO22 HEPATHER (Pol 2015 EASL) (153)	See GT1 TN															
SMV+Peg-IFN+RBV RGT	PROMISE (HPC3007) (SmPC and Forns 2014 (26, 115))	260	52	93.5	2.7	6.42	84.4	15.6 (F4)/15.6 (C)	100	100	42.3	57.3	-	-	-	-	-
Peg-IFN+RBV 48w	REALIZE (Study C216) (TVR SmPC and Zeuzem 2011 (32, 122))	132	50	89	8	6.6±0.05	77	23 (C)	100	100	45	45	-	-	-	-	-
GT2 TN (NC and CC)																	
SOF/VEL 12w	ASTRAL-2 (Section 4.3)	134	57	93	4	6.5±0.78	NR	14 (C)	14	-	-	-	100	-	-	-	-
SOF+RBV 12w	ASTRAL-2 (Section 4.3)	132	57	84	9	6.4±0.74	NR	14 (C)	15	-	-	-	100	-	-	-	-
Peg-IFN+RBV 24w	FISSION (SmPC and Lawitz et al, 2013 (19, 24)) Informs Bucher indirect comparison with SOF/VEL (See Section 4.10.9.1)	See GT3 TN															

Regimen of interest to decision problem[†]	Source	N	Age	Race		Viral load (RNA IU/mL)	Liver histology, %		TE, %	Genotype, %							
			Mean	White %	Black %	Mean (SD)	F0-3	F4/ C/ DCC		1	1a	1b	2	3	4	5	6
GT2 TE (NC and CC)																	
SOF/VEL 12w	ASTRAL-2 (Section 4.3)	See GT2 TN															
SOF+RBV 12w	ASTRAL-2 (Section 4.3)	See GT2 TN															
Peg-IFN+RBV 24w	Lagging 2013/Shoeb 2014	See GT3 TE															
GT4/5/6 TN (NC and CC)																	
SOF/VEL 12w	ASTRAL-1 (Section 4.3)	See GT1 TN															
LDV/SOF 12w	Study 1119 (SmPC and Abergel 2015 (155)) (GT4)	22	52	86	NR	6.0	NR	5 (C)	0	-	-	-	-	-	100	-	-
	Study 1119 (SmPC and Abergel 2015 (155)) (GT5)	21	61	100	0	6.2	NR	14 (C)	0	-	-	-	-	-	-	100	-
	Gane 2015 (98) (GT6)	25	51	16	0 (84 Asian)	6.7±0.67	NR	8 (C)	8	-	-	-	-	-	-	-	100
OBV/PTV/RTV+RBV 12w	PEARL-I (Hezode 2015 (110))	42	44	NR	NR	6.1±0.6	100	0 (F4)/ 0 (C)	0	-	-	-	-	-	100	-	-
OBV/PTV/RTV+RBV 24w	No data																
SOF+Peg-IFN+RBV 12w	NEUTRINO	See GT1 TN (NC and CC)															

Regimen of interest to decision problem[†]	Source	N	Age	Race		Viral load (RNA IU/mL)	Liver histology, %		TE, %	Genotype, %							
			Mean	White %	Black %	Mean (SD)	F0-3	F4/ C/ DCC		1	1a	1b	2	3	4	5	6
SMV+Peg-IFN+RBV RGT	RESTORE (HPC3011) (Moreno 2015 (156))	35 (GT4)	47	60	40	6.19[¶]	94	6 (F4)/ 9 (C)	0	-	-	-	-	-	100	-	-
DCV+Peg-IFN+RBV 24w	COMMAND-4 (AI444042) (Hezode, 2015 (90))	82 (GT4)	48.5[¶]	73.2	22.0	5.8±0.78	NR	11 (C)	0	-	31.7	-	-	-	68.3	-	-
Peg-IFN+RBV 48w	COMMAND-4 (AI444042) (Hezode, 2015 (90))	42 (GT4)	50[¶]	85.7	11.9	5.7±0.61	NR	9.5 (C)	0	-	0	-	-	-	100	-	-
GT4/5/6 TE (NC and CC)																	
SOF/VEL 12w	ASTRAL-1 (Section 4.3)	See GT1 TN															
LDV/SOF 12w	Study 1119 (SmPC and Abergel 2015 (155)) (GT4)	22	50	77	NR	6.3	NR	41 (C)	100	-	-	-	-	-	100	-	-
	Study 1119 (SmPC and Abergel 2015 (155)) (GT5)	20	64	100	0	6.6	NR	30 (C)	100	-	-	-	-	-	-	100	-
	Gane 2015 (98) (GT6)	See GT4/5/6 TN (NC and CC)															
OBV/PTV/RTV+RBV 12w	PEARL-I (Hezode 2015 (110))	49	51	NR	NR	6.3±0.5	100	0 (F4)/ 0 (C)	100	-	-	-	-	-	100	-	-
OBV/PTV/RTV+RBV 24w	No data																
SOF+Peg-IFN+RBV 12w	Assumed equal to NEUTRINO (mainly GT4)	See GT1 TN															

Regimen of interest to decision problem†	Source	N	Age	Race		Viral load (RNA IU/mL)	Liver histology, %		TE, %	Genotype, %							
			Mean	White %	Black %	Mean (SD)	F0-3	F4/ C/ DCC		1	1a	1b	2	3	4	5	6
SMV+Peg-IFN+RBV RGT	RESTORE (HPC3011) (Moreno 2015 (156))	72 (GT4)	49§	77.8	22.2	6.10¶§	59	41 (F4)/ 41 (C)	100	-	-	-	-	-	100	-	-
DCV+Peg-IFN+RBV 24w	No data; assume same as COMMAND-4 for TN	See GT4/5/6 TN (NC and CC)															
Peg-IFN+RBV 48w	No data; assume same as COMMAND-4 for TN	See GT4/5/6 TN (NC and CC)															
Any GT with DCC (TN/TE)																	
SOF/VEL+RBV 12w	ASTRAL-4 (Section 4.11.3)	87	58	91	6	5.8±0.6	NR	100 (DCC)	54	78	62	16	5	15	2	-	0
LDV/SOF+RBV 12w	SOLAR-1 (SmPC & Charlton 2015 (21, 128))	23 (CPT C)	58¶	91	9	5.6±0.6	NR	100 (DCC)	48	91	65	26	-	-	9	-	-

BMI, body mass index; BOC, boceprevir; C, cirrhosis; CPT, Child-Pugh-Turcotte; DCC, decompensated cirrhosis; GT, genotype; LDV, ledipasvir; NR, not reported; PR, pegylated interferon + ribavirin; RNA, ribonucleic acid; SD, standard deviation; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
† Where NICE recommendations restrict a regimen to a subgroup by fibrosis or cirrhotic status this is included in parentheses after the regimen name; ‡ Scores not available for 3 patients; ¶ Median; § Not available for TE group overall, data are for TN+TE patients.

4.10.9.1 Bucher indirect comparison

A Bucher method of indirect treatment comparison (ITC) for SOF/VEL versus Peg-IFN+RBV was investigated to inform SVR rates in the economic model for GT2 treatment-naïve patients (non-cirrhotic and cirrhotic). This was carried out using data from the FISSION and ASTRAL-2 studies, with the aim of allowing a comparison of SOF/VEL with Peg-IFN+RBV, using SOF+RBV as a common comparator/bridge. The OR obtained from the ITC in treatment-naïve, non-cirrhotic patients was 28.859 (95% CI: 1.922, 433.393), which is logical when compared with the trial level estimates of treatment effect.

However, it was not considered credible to use this OR in the economic model, therefore the RD was investigated as an alternative outcome measure. There is little in the literature to guide decisions around the choice of scales by which to perform meta-analyses and ITCs, however, as a RD is symmetric, it can be considered acceptable to perform an ITC using this as the outcome measure. In addition, RDs are relatively easy to interpret, whereas ORs can be more complex.

In GT2, treatment-naïve, non-cirrhotic patients, the ITC resulted in an 18.41% positive difference in SVR rate for SOF/VEL versus Peg-IFN+RBV (Table 41). The economic model therefore uses an SVR rate of 99.00% for SOF/VEL (as the reference treatment) and a derived SVR rate of 80.59% for Peg-IFN+RBV.

Table 41: ITC for SOF/VEL versus Peg-IFN+RBV (GT2, treatment-naïve, non-cirrhotic patients)

Trial	Comparison	Treatment SVR (n/N)	SOF+RBV SVR (n/N)	Difference
ASTRAL-2 (See Section 4.7.2)	SOF/VEL vs SOF+RBV	99.00% (99/100)	95.83% (92/96)	+3.17%
FISSION (SmPC and Lawitz et al, 2013 (19, 24))	Peg-IFN+RBV vs SOF+RBV	81.48% (44/54)	96.72% (59/61)	-15.24%
ITC: SOF/VEL vs Peg-IFN+RBV [RD]				**+18.41%**

ITC, indirect treatment comparison; Peg-IFN, pegylated interferon; RBV, ribavirin; RD, relative difference; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

In GT2, treatment-naïve, cirrhotic patients, the ITC resulted in a 28.46% positive difference in SVR rate for SOF/VEL versus Peg-IFN+RBV (Table 42). The economic model therefore uses an SVR rate of 100.00% for SOF/VEL (as the reference treatment) and a derived SVR rate of 71.54% for Peg-IFN+RBV.

Table 42: ITC for SOF/VEL versus Peg-IFN+RBV (GT2, treatment-naïve, cirrhotic patients)

Trial	Comparison	Treatment SVR (n/N)	SOF+RBV SVR (n/N)	Difference
ASTRAL-2 (See Section 4.7.2)	SOF/VEL vs SOF+RBV	100.00% (15/15)	93.33% (14/15)	+6.67%
FISSION (SmPC and Lawitz et al, 2013 (19, 24))	Peg-IFN+RBV vs SOF+RBV	61.54% (8/13)	83.33% (10/12)	-21.79%
ITC: SOF/VEL vs Peg-IFN+RBV [RD]				**+28.46%**

ITC, indirect treatment comparison; Peg-IFN, pegylated interferon; RBV, ribavirin; RD, relative difference; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

4.11 *Non-randomised and non-controlled evidence*

4.11.1 *List of relevant non-randomised and non-controlled evidence*

ASTRAL-4 is the pivotal Phase III trial for SOF/VEL for the treatment of CHC of any genotype in adult patients with decompensated cirrhosis (confirmed CPT class B at screening), and is described in detail in Section 4.11.3 through 4.11.7. ASTRAL-5 is an ongoing study in patients co-infected with HCV and HIV; preliminary data was presented at EASL in April 2016, and is briefly described in Section 4.11.8.

Table 43: List of relevant non-RCTs

Study number (acronym)	Objective	Population	Intervention	Comparator	Primary study reference	Justification for inclusion
GS-US-342-1137 (ASTRAL-4)	• To evaluate the efficacy of treatment with SOF/VEL+/-RBV for 12 weeks and SOF/VEL for 24 weeks in patients with CHC and CPT class-B cirrhosis, as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of each treatment regimen	• HCV GT1-6 • Treatment-naïve and treatment-experienced • Decompensated cirrhosis (classified as CPT class B)	• SOF/VEL for 12 weeks • SOF/VEL+RBV for 12 weeks • SOF/VEL for 24 weeks	Not applicable	Curry et al, 2015 (71) Supporting information from CSR (157)	Pivotal Phase III trial for SOF/VEL treatment of HCV GT1-6 patients with decompensated cirrhosis
ASTRAL-5 (ongoing)	• To evaluate the efficacy and safety of treatment with SOF/VEL for 12 weeks in patients co-infected with HIV and HCV	• HCV genotypes 1–6 and HIV • Treatment naïve or experienced • No cirrhosis and compensated cirrhosis	• SOF/VEL for 12 weeks	Not applicable	Wyles et al, 2016 (158)	Phase III trial for SOF/VEL treatment of HCV/HIV co-infected patients

CPT, Child-Pugh-Turcotte; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

4.11.2 *List of non-RCTs excluded from further discussion*

Three Phase II randomised, open-label trials (Pianko et al, 2015 (72), Everson et al, 2015 (73), ELECTRON-2 (74)) assessed the efficacy and safety of SOF plus different doses of VEL with and without RBV for the treatment of adult patients with CHC. These were dosing studies which informed the selection of the VEL dose of 100 mg and treatment duration of 12 weeks as the most efficacious and appropriate for evaluation in the Phase III ASTRAL trials. These Phase II studies do not provide any new data, comparative or otherwise, that are not provided by the Phase III ASTRAL trials. As such these Phase II studies have been excluded from further discussion in relation to SOF/VEL efficacy and safety. However, these studies were considered for the feasibility of their inclusion in evidence networks for the purpose of performing NMA, as described previously in Section 4.10.

Table 44: List of non-RCTs excluded from further discussion

Trial no. (acronym)	Objectives	Population	Intervention	Comparator	Primary study ref.
NCT01909804 (Pianko et al)	To assess the efficacy and safety of SOF plus VEL, with and without RBV, in treatment-experienced patients.	• HCV GT1 and GT3 • Treatment-experienced • No cirrhosis and compensated cirrhosis	• SOF 400mg + VEL 25mg for 12 weeks • SOF 400mg + VEL 25mg + RBV for 12 weeks • SOF 400mg + VEL 100mg for 12 weeks • SOF 400mg + VEL 100mg + RBV for 12 weeks	Not applicable	Pianko et al, 2015 (72)
NCT01858766 (Everson et al)	To assess the safety and efficacy of SOF with VEL in patients infected with HCV GT1–6.	• HCV GT1-6 • Treatment-naïve • No cirrhosis	• SOF 400mg + VEL 25mg for 12 weeks • SOF 400mg + VEL 25mg + RBV for 12 weeks • SOF 400mg + VEL 100mg for 12 weeks • SOF 400mg + VEL 100mg + RBV for 12 weeks	Not applicable	Everson et al, 2015 (73)

Trial no. (acronym)	Objectives	Population	Intervention	Comparator	Primary study ref.
ELECTRON-2	To evaluate the efficacy and safety of SOF plus VEL ± RBV for 8 weeks in treatment-naïve HCV GT 3 patients without cirrhosis	• HCV GT3 • Treatment-naïve • No cirrhosis	• SOF 400mg + VEL 25mg for 8 weeks • SOF 400mg + VEL 25mg + RBV for 8 weeks • SOF 400mg + VEL 100mg for 8 weeks • SOF 400mg + VEL 100mg + RBV for 8 weeks	Not applicable	Gane et al, AASLD 2014 (74)

GT, genotype; HCV, hepatitis C virus; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

4.11.3 *Summary of methodology of the relevant non-randomised and non-controlled evidence*

Table 45: Comparative summary of methodology

Trial no. (acronym)	GS-US-342-1137 (ASTRAL-4) CHC GT1–6 with decompensated cirrhosis
Study objective	• To evaluate the efficacy of treatment with SOF/VEL+/-RBV for 12 weeks and SOF/VEL for 24 weeks in patients with CHC and CPT class-B cirrhosis, as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of each treatment regimen
Location	47 sites in the United States.
Design	Multicentre, randomised, open-label, Phase III.
Duration of study	Treatment duration: 12 or 24 weeks depending on treatment assignment. Follow-up: up to 24 weeks.
Method of randomisation	An IWRS was employed to manage patient randomisation and treatment assignment. Randomisation was stratified by: • Genotype (1, 2, 3, 4, 5, 6, indeterminate)
Method of blinding (care provider, patient and outcome assessor)	The study was open-label.
Intervention(s) (n=) and comparator(s) (n=)	Patients were randomised in a 1:1:1 ratio to: • SOF/VEL for 12 weeks (n=90) • SOF/VEL+RBV for 12 weeks (n=87) • SOF/VEL for 24 weeks (n=90) Patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily with or without RBV. RBV was administered orally twice daily, with the dose determined according to body weight (1,000 mg daily in patients with a body weight <75 kg, and 1,200 mg daily in patients with a body weight ≥75kg).
Permitted and disallowed concomitant medications	Concomitant medications taken within 30 days of screening, up to and including 30 days after the last dose of study drug, were recorded. The following were prohibited from 28 days prior to the baseline/Day 1 visit through the EOT visit: • Investigational agents or devices for any indication • Drugs disallowed according to prescribing information of SOF or RBV Concomitant use of medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e. P-glycoprotein) which may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug(s) or these medications. Examples of representative medications that were prohibited from 21 days prior to baseline/Day 1 through EOT are listed in the clinical study protocol. Medications for disease conditions excluded from the protocol (e.g., HIV-1, active cancer, transplantation) were not listed as concomitant medications and were disallowed in the study.
Assessments performed	All patients were to have study visits at screening, baseline, and on-treatment at the end of week 1, 2, 4, 6, 8, 10 and 12. Patients in the SOF/VEL 24 week group had additional on-treatment visits at the end of week 16, 20 and 24. Post-treatment visits were to occur at week 4, 12 and 24 (if applicable).

Trial no. (acronym)	GS-US-342-1137 (ASTRAL-4) CHC GT1–6 with decompensated cirrhosis
	Screening assessments were to be completed within 28 days (42 days if liver biopsy or additional HCV genotype testing required) of the baseline/Day 1 visit. All patients had to complete post-treatment week 4 and week 12 assessments, regardless of treatment duration. Patients with HCV RNA <LLOQ at post-treatment week 12 had to complete post-treatment week 24 assessments, unless confirmed viral relapse occurred. Assessments included: • Complete physical examination (screening, baseline, weeks 12 and 24 [SOF/VEL 24 week group only]) • Body weight (screening, baseline, weeks 4, 12 and 24 [SOF/VEL 24 week group only], post-treatment weeks 12 and 24) • Vital signs† (every visit) • 12-lead ECG (screening, baseline, weeks 1 and 12, and week 24 [SOF/VEL 24 week group only]) • AEs and concomitant medications (every visit) • Serum HCV RNA (every visit) • IL28B genotyping (screening) • Viral RNA sequencing and phenotyping (every visit except screening) • HCV genotype and subtype (screening only) • Blood samples for haematology, chemistry, coagulation and an assessment of presence of ascites and hepatic encephalopathy at all visits were used to inform CPT and MELD scores • HRQL surveys (baseline, weeks 4, 8, 12, and weeks 16, 20 and 24 [SOF/VEL 24 week group only], post-treatment weeks 4, 12 and 24)
Primary outcomes (including scoring methods and timings of assessments)	SVR12, defined as HCV RNA <LLOQ, 12 weeks after the end of treatment, in the FAS population. The LLOQ was 15 IU/mL.
Secondary outcomes (including scoring methods and timings of assessments)	• Proportion of patients with SVR (HCV RNA<LLOQ) at 4 weeks and 24 weeks after end of treatment (SVR4 and SVR24) • The proportion of patients with HCV RNA<LLOQ on treatment by study visit • HCV RNA change from baseline through EOT • Change in CPT score and MELD score in patients who achieved and did not achieve SVR12: ○ CPT scores range from 5 to 15, and were calculated as the sum of the scores for five items (total bilirubin, serum albumin, INR, ascites and hepatic encephalopathy) where each item was attributed a score of 1-3. CPT score 5 or 6=CPT Class A; CPT score 7, 8, or 9=CPT Class B; CPT score 10, 11, 12, 13, 14, or 15=CPT Class C. ○ MELD score=10 × {[0.957 × Ln(Scr)] + [0.378 × Ln(Tbil]) + [1.12 × Ln(INR)] + 0.643)}, where Scr=serum creatinine (in mg/dL), Tbil=total bilirubin (in mg/dL), INR=international normalised ratio, and Ln=natural log. If any lab value was <1.0, then it was set to 1.0 in the calculation. If the patient received dialysis at least twice in the previous week, then Scr was set to 4.0 mg/dL in the above formula. MELD scores range from 6 to 40 with higher scores indicating more advanced liver disease. • 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.

Trial no. (acronym)	GS-US-342-1137 (ASTRAL-4) CHC GT1–6 with decompensated cirrhosis
	• Characterisation of drug resistance at baseline, during and after therapy: Deep sequencing of the HCV NS5A and NS5B coding regions was performed on samples obtained from all patients at baseline and again for all patients with virologic failure. Sequences that were obtained at the time of virologic failure were compared with sequences from baseline samples to detect resistance-associated variants that emerged during treatment. Resistance-associated variants that were present in >1% of sequence reads were reported. • ALT normalisation • HRQL (SF-36, CLDQ-HCV, FACIT-F and WPAI)

AE, adverse event; CHC, chronic hepatitis C; CLDQ, Chronic Liver Disease Questionnaire; CPT, Child-Pugh-Turcotte; ECG, electrocardiogram; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; FACIT-F, Fatigue Index; FAS, full analysis set; GCSF, granulocyte colony stimulating factor; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQL, Health Related Quality of Life; INR, International Normalised Ratio; IWRS, interactive web response system; LLOQ, lower limit of quantitation; MELD, Model for End-Stage Liver Disease; RBV, ribavirin; RNA, ribonucleic acid; SF-36, 36-Item Short-Form Survey; SOF, sofosbuvir; SVR, sustained virologic response; TPO, thrombopoietin; VEL, velpatasvir; WPAI, Work Productivity and Activity Impairment.
† Vital signs include resting blood pressure, pulse, respiratory rate and temperature.

4.11.3.1 Eligibility criteria

ASTRAL-4 enrolled adult patients with confirmed CHC of any genotype with decompensated cirrhosis (confirmed CPT class B at screening) (Table 46).

Table 46: Detailed eligibility criteria

Trial no. (acronym)	GS-US-342-1137 (ASTRAL-4) CHC GT1–6 with decompensated cirrhosis
Inclusion criteria	
HCV genotype	Not specified as an inclusion criteria but patients with HCV GT1, GT2, GT3, GT4, and GT6 were enrolled.
Treatment experience	Not specified as an inclusion criteria but patients who were HCV treatment-naïve or treatment-experienced were enrolled.
Cirrhosis permitted	***Presence of cirrhosis in all patients*** • 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 ○ Fibroscan showing cirrhosis or a result >12.5 kPa • Confirmed CPT class B (7–9) at screening • If listed for liver transplant, baseline is expected to be ≥12 weeks prior to transplant
General inclusion criteria	• Willing and able to provide written informed consent • Aged ≥18 years • HCV RNA≥10^4 IU/mL at screening • Chronic HCV infection (≥6 months) determined by prior medical history or liver biopsy • Females of childbearing potential must have had a negative serum pregnancy test at screening and a negative urine pregnancy test on baseline prior to randomisation • Male patients and female patients of childbearing potential who engage in

Trial no. (acronym)	GS-US-342-1137 (ASTRAL-4) CHC GT1–6 with decompensated cirrhosis
	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 • 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 or currently under evaluation for a potentially clinically significant illness (other than HCV or co-morbidities associated with advanced liver disease except as noted below) or any other major medical disorder that may interfere with patient treatment, assessment or compliance with the protocol ○ Gastrointestinal disorder or post-operative condition that could interfere with the absorption of the study drug ○ Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy ○ Solid organ transplantation ○ Significant pulmonary disease, significant cardiac disease or porphyria ○ Psychiatric hospitalisation, suicide attempt, and/or a period of disability as a result of psychiatric illness within the last 5 years. Patients with psychiatric illness (other than the prior mentioned conditions) that was well-controlled on a stable treatment regimen for ≥12 months prior to randomisation or had not required medication in the last 12 months may be included ○ 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 are not eligible ○ Significant drug allergy (e.g. anaphylaxis or hepatotoxicity) • Inability to exclude HCC by imaging within 6 months of baseline (including indeterminate hepatic nodule meeting OPTN Class 5 criteria, defined by arterial enhancement with washout on portal venous/delayed phase or rate of growth maximum diameter increase in the absence of ablative therapy by 50% or more documented on serial MRI or CT obtained <6 months apart) • Infection with HBV or HIV • ECG at screening with clinically significant abnormalities • Prior exposure to SOF or other nucleotide analogue HCV NS5B inhibitor or any HCV NS5A inhibitor • Use of GM-CSF, epoetin alpha or other haematopoietic stimulating agents within 3 months of screening • History of clinically significant medical conditions associated with other chronic liver disease (e.g., hemochromatosis, autoimmune hepatitis, Wilson's disease, α-1-antitrypsin deficiency, alcoholic liver disease, non-alcoholic steatohepatitis, or toxin exposures) • Medical justification for any MELD exception points (such as for HCC, current hepatopulmonary syndrome, intractable encephalopathy, or any other reason) • Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent >10 mg/day) • Infection requiring systemic antibiotics at the time of screening • Active variceal bleeding within 6 months

Trial no. (acronym)	GS-US-342-1137 (ASTRAL-4) CHC GT1–6 with decompensated cirrhosis
	• Prior placement of a portosystemic shunt (such as transjugular intrahepatic portosystemic shunt) • Laboratory parameters, including: ○ Haemoglobin <10 g/dL ○ Platelets ≤30,000/mm^3 ○ ALT, AST, or alkaline phosphatase ≥10 x ULN ○ Sodium <125 mEq/L ○ Total bilirubin >5 mg/dL ○ CLcr <50 mL/min • Participation in a clinical study with an investigational drug or biologic within 1 month prior to screening visit • Clinically-relevant alcohol or drug abuse within 12 months of screening • Contraindication to RBV therapy • Use of any prohibited concomitant medications described in Table 12 • Known hypersensitivity to VEL, RBV, SOF, or formulation recipients

ALT, alanine aminotransferase; APRI, ratio index; AST, aspartate aminotransferase; CHC, chronic hepatitis C; CL_{cr}, creatinine clearance; CPT, Child-Pugh-Turcotte; CT, computed tomography; ECG, electrocardiogram; EOT, end of treatment; GM-CSF, granulocyte-macrophage colony-stimulating factor; $bHbA_{1c}$, haemoglobin A_{1c}; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus, IFN, interferon; INR, International Normalised Ratio of prothrombin time; MRI, magnetic resonance imaging; OPTN, Organ Procurement and Transplantation Network; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; ULN, upper limit of the normal range; VEL, velpatasvir.

4.11.4 *Statistical analysis of the non-randomised and non-controlled evidence*

Analysis sets

FAS: Patients who were randomised into the study and received at least one dose of study drug. Patients were grouped by the treatment group to which they were randomised. The FAS was the primary analysis set for efficacy analyses.

SAS: Patients who were randomised into the study and received at least one 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.

Table 47: Summary of statistical analyses

Trial no. (acronym)	GS-US-342-1137 (ASTRAL-4) CHC GT1–6 with decompensated cirrhosis
Hypothesis objective	In the primary efficacy hypothesis, the rate of SVR in each of the three treatment groups was compared with an assumed spontaneous rate of 1%.
Statistical analysis of primary endpoint	• SVR rates for each treatment group were compared with the assumed spontaneous rate using the two-sided exact one-sample binomial test with Bonferroni alpha adjustment • Point estimates and two-sided 95% exact CIs based on the Clopper–Pearson method are provided for SVR rates for the three treatment groups, as well as according to HCV genotype • The study was not designed or powered to detect significant differences in rates of SVR between treatment groups. However, a post-hoc pairwise comparison of SVR rates among the three treatment groups was performed, for which point

Trial no. (acronym)	GS-US-342-1137 (ASTRAL-4) CHC GT1–6 with decompensated cirrhosis
	estimates, corresponding 98.3% CIs, and p values (using the Cochran–Mantel–Haenszel test) were calculated. The choice of 98.3% CIs, rather than 95%, reflected the need for three pairwise comparisons
Statistical analysis of secondary efficacy endpoints	• Proportion of patients with SVR4 and SVR24: SVR4 results were summarised. SVR24 results are not currently available but will be included in the final CSR • Analyses of changes in CPT and MELD scores from baseline to post-treatment week 12: proportion of patients with each change from baseline score (-3, -2, -1, 0, 1, etc.) and with no change, increase or decrease. The analysis of change in the MELD score was also performed separately for patients with a baseline score of <15 and those with a baseline score of ≥15 • 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 proportion of patients with HCV RNA <LLOQ at each visit by treatment group, overall and broken down by HCV genotype. 'HCV RNA <LLOQ' was split into two categories: <LLOQ TND (for patients with target not detected) and <LLOQ detected (for patients with <LLOQ) • HCV RNA absolute values and change from baseline: Summary statistics are presented by visit through to EOT overall and broken down by HCV. Imputation rules (described further in "data management, patient 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 • Virologic failure: Descriptively summarised as 'on-treatment virologic failure' and 'relapse'. 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 patients in the FAS. Virologic outcomes were also provided by cirrhosis status and prior treatment experience. All virologic failure results were provided for each treatment group overall and broken down by HCV genotype. • 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 • ALT normalisation: similar methodology to the analyses of HCV RNA<LLOQ, using a missing=excluded analysis. Only patients with ALT >ULN range at baseline were to be included in the analysis • 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 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
Sample size, power calculation	A sample size of 75 patients in each treatment group was calculated to provide a power of 99% to detect an improvement of ≥40 percentage points in the rate of SVR over the assumed spontaneous rate of 1%, using the two-sided exact one-sample binomial test at a significance level of 0.0167.
Data management, patient	• Values for missing data were not imputed for any outcomes except HCV RNA and post-treatment HRQL data

Trial no. (acronym)	GS-US-342-1137 (ASTRAL-4) CHC GT1–6 with decompensated cirrhosis
withdrawals	• For categorical HCV RNA data, if a data point was missing, and was preceded and followed by values that were a success (<LLOQ TND and/or <LLOQ detected) then the missing data point was termed a bracketed success; otherwise the data point was termed a bracketed failure (≥LLOQ detected) • Patients with missing data due to premature discontinuation of the study had missing data imputed up to the time of their last dose (if last dose was on-treatment). If study day associated with the last dose was ≥the lower bound of a visit window, and the value at visit was missing, then the value was imputed. If the study day associated with the last dose was <the lower bound of the visit window, then the on-treatment value at that visit remained missing • If HCV RNA 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 1 IU/mL. No other imputations were performed for continuous data • For HRQL data, missing data at on-treatment visits and 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

CHC, chronic hepatitis C; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CSR, clinical study report; 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; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected; VEL, velpatasvir.

4.11.5 *Participant flow in the studies*

4.11.5.1 Patient disposition (ASTRAL-4)

The CONSORT flow chart for ASTRAL-4 is presented in Figure 12. The primary analyses in ASTRAL-4 was based on the FAS.

In ASTRAL-4, 438 patients were initially screened. Of these, 268 patients were randomised and 267 received at least one dose of the study drug (FAS); 90 in the SOF/VEL 12 week group, 87 in the SOF/VEL+RBV 12 week group and 90 in the SOF/VEL 24 week group.

Reasons for premature discontinuations are presented in Table 48.

Figure 12: Patient disposition in ASTRAL-4

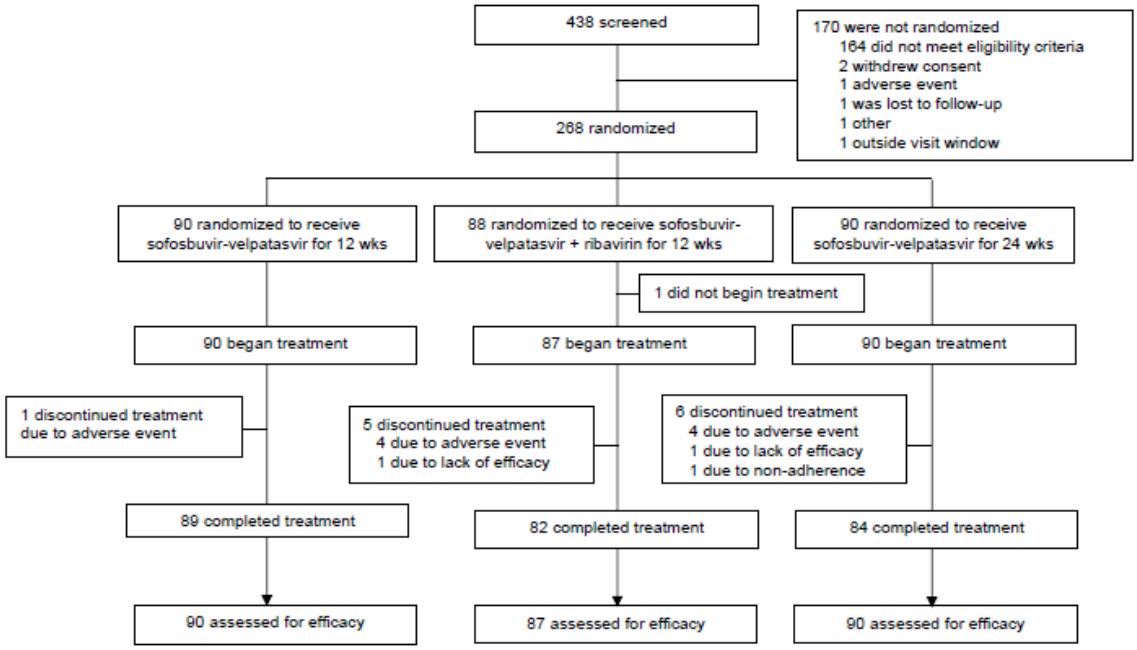


Table 48: Reasons for premature discontinuation of study treatment in ASTRAL-4 (FAS)

	SOF/VEL 12 weeks N=90	SOF/VEL+RBV 12 weeks N=87	SOF/VEL 24 weeks N=90	Total N=267
Total premature discontinuations, n (%)	1 (1.1)	5 (5.7%)	6 (6.7)	12 (4.5)
Adverse event, n (%)	1 (1.1)	4 (4.6)	4 (4.4)	9 (3.4)
Lack of efficacy, n (%)	0	1 (1.1)	1 (1.1)	2 (0.7)
Non-compliance with study drug, n (%)	0	0	1 (1.1)	1 (0.4)

RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

4.11.5.2 Baseline characteristics and demographics (ASTRAL-4)

Patient characteristics at baseline for ASTRAL-4 are presented in Table 49.

In ASTRAL-4, demographics and baseline characteristics were generally balanced across both treatment groups (Table 49). Overall, the majority of patients were male (70%) and white (90%), with a mean age of 58 years (range: 40–73). Baseline disease characteristics were also generally balanced across both treatment groups. Overall, 60% of patients had HCV GT1a, 18% GT1b, 4% GT2, 15% GT3, 3% GT4, and <1% GT6. No patients had HCV GT5.

A total of 6% of patients were black, and 55% were HCV treatment-experienced, with the majority having been treated with either a PI-based regimen (19%) or [redacted] The median baseline CPT score was 8 (range: 5–10), the median baseline MELD score was 10 (range, 6–24), and the median creatinine clearance (estimated glomerular filtration rate) was 84.7 ml per minute (range: 15–198). The majority of patients (95%) had a baseline MELD score of ≤15. All patients had CPT class B (CPT score 7–9) cirrhosis at screening; however, 27 patients (10%) had CPT class A (CPT score 5–6) or CPT class C (CPT score 10–15) cirrhosis

at treatment baseline, which reflects the dynamic changes in cirrhotic status (CPT scoring) in this population.

Table 49: Characteristics of participants in ASTRAL-4 (FAS)

Characteristic	SOF/VEL 12 weeks N=90	SOF/VEL+RBV 12 weeks N=87	SOF/VEL 24 weeks N=90
Mean age (range), years	58 (42–73)	58 (40–71)	58 (46–72)
Male, n (%)	57 (63)	66 (76)	63 (70)
Mean BMI (range), kg/m2[†]	31 (17–56)	30 (20–55)	30 (18–50)
Race, n (%)[‡]			
White	79 (88)	79 (91)	81 (90)
Black	6 (7)	5 (6)	6 (7)
Asian	3 (3)	0	2 (2)
Other	2 (2)	3 (3)	1 (1)
HCV genotype			
1a	50 (56)	54 (62)	55 (61)
1b	18 (20)	14 (16)	16 (18)
2	4 (4)	4 (5)	4 (4)
3	14 (16)	13 (15)	12 (13)
4	4 (4)	2 (2)	2 (2)
6	0	0	1 (1)
Mean HCV RNA±SD, log10 IU/mL	6.0±0.5	5.8±0.6	5.9±0.6
HCV RNA≥800,000 IU/mL, n (%)	59 (66)	45 (52)	45 (50)
IL28B genotype, n (%)			
CC	20 (22)	22 (25)	20 (22)
CT	51 (57)	46 (53)	49 (54)
TT	19 (21)	19 (22)	19 (21)
Missing data	0	0	2 (2)
CPT score, n (%)[§]			
≤6	3 (3)	6 (7)	7 (8)
7	36 (40)	23 (26)	21 (23)
8	31 (34)	41 (47)	34 (38)
9	19 (21)	13 (15)	22 (24)
10	1 (1)	4 (5)	6 (7)
MELD score, n (%)[¶]			
<10	36 (40)	29 (33)	26 (29)
10–15	50 (56)	54 (62)	59 (66)
≥16	4 (4)	4 (5)	5 (6)
Ascites, n (%)			
None	16 (18)	22 (25)	15 (17)
Mild or moderate	72 (80)	61 (70)	74 (82)

Characteristic	SOF/VEL 12 weeks N=90	SOF/VEL+RBV 12 weeks N=87	SOF/VEL 24 weeks N=90
Severe	2 (2)	4 (5)	1 (1)
Mean estimated glomerular filtration rate (range), ml/min††	89 (15–169)	90 (50–167)	90 (43–198)
Previous HCV treatment, n (%)			
No	32/90 (36)	40/87 (46)	48/90 (53)
Yes	58/90 (64)‡‡	47/87 (54)	42/90 (47)
Type of previous HCV treatment, n/total (%)			
PI+Peg-IFN+RBV	9/58 (16)	12/47 (26)	7/42 (17)
Peg-IFN+RBV	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Missing data	[redacted]	[redacted]	[redacted]

BMI, body mass index; CPT, Child-Pugh-Turcotte; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; Peg-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; VEL, velpatasvir.

† BMI is the weight in kg divided by the height squared in metres; ‡ race was self-reported; § CPT score ranges from 5 to 15, with higher scores indicating more advanced liver disease; ¶ MELD score ranges from 6 to 40, with higher scores indicating more advanced disease; †† the estimated glomerular filtration rate was calculated with the use of the Cockcroft‑Gault equation; ‡‡ data regarding previous treatment were missing for one patient.

4.11.6 *Quality assessment of the relevant non-randomised and non-controlled evidence*

ASTRAL-4		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	An interactive web response system was used	Yes
Was the concealment of treatment allocation adequate?	An interactive web response system was used	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Demographic and baseline clinical characteristics were generally well balanced	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Study was open-label. SVR is a laboratory value and so shouldn't be prone to bias	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were small differences in discontinuation rates between arms which may have been expected due to the use of RBV or longer treatment durations (one, five and six discontinuations in the SOF/VEL 12 week, SOF/VEL+RBV 12 week and SOF/VEL 24 week arms, respectively). Reasons for drop outs were provided	No

ASTRAL-4		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	-	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?	Modified ITT was used. The analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data	Yes

FAS, full analysis set; ITT, intent-to-treat; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

4.11.7 *Clinical effectiveness results of the relevant non-randomised and non-controlled evidence (ASTRAL-4)*

Primary and secondary efficacy results for ASTRAL-4 are presented in Table 50.

4.11.7.1 Primary efficacy results: SVR12

Among patients in the overall trial population (with GT1, GT2, GT3, GT4, or GT6 HCV infection) the SVR rate 12 weeks after treatment was 83.3% [redacted] with SOF/VEL for 12 weeks, 94.3% [redacted] with SOF/VEL+RBV for 12 weeks, and 85.6% [redacted] with SOF/VEL for 24 weeks.

All three treatment groups met the pre-specified primary efficacy endpoint, with SVR12 rates that were significantly superior to the assumed spontaneous rate of HCV clearance of 1% ($p<0.001$ for all three groups).

SVR12 by genotype

Among patients with HCV GT1 (n=207), the SVR12 rate was 88.2% for those who received SOF/VEL for 12 weeks, 95.6% for those who received SOF/VEL+RBV, and 91.5% for those who received SOF/VEL for 24 weeks (Table 51).

Among the next largest population of patients by genotype – those with HCV GT3 (n=39) – the SVR12 rates were 84.6% for SOF/VEL+RBV for 12 weeks and 50% for both SOF/VEL monotherapy groups.

All patients with HCV GT2, GT4, or GT6 (n=21) had an SVR12 except for one patient with HCV GT2 who was randomised to the SOF/VEL 24 week group; this patient died of liver failure after completing 28 days of treatment.

Post-hoc analysis

Post hoc analyses did not detect any significant differences in SVR12 rates among the three treatment groups (significance level=0.0167).

- SOF/VEL+RBV 12 weeks versus SOF/VEL 24 weeks: treatment difference 8.7% (98.3% CI: -2.2%, 19.6%), p=0.056

- SOF/VEL 12 weeks versus SOF/VEL 24 weeks: treatment difference -2.2% (98.3% CI: -15.3%, 10.9%), p=0.68
- SOF/VEL 12 weeks versus SOF/VEL+RBV 12 weeks: treatment difference -10.9% (98.3% CI: -22.3%, 0.4%), p=0.022

Table 50: Summary of response during and after treatment in ASTRAL-4 (FAS)

Response	SOF/VEL 12 weeks N=90	SOF/VEL+RBV 12 weeks N=87	SOF/VEL 24 weeks N=90
HCV RNA<LLOQ			
During treatment, n/N (%)[†]			
At week 2	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
At week 4	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
At week 6	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
At week 8	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
[redacted]			
At week 4 (SVR4)	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
At week 12 (SVR12)	75/90 (83.3)	82/87 (94.3)	77/90 (85.6)
95% CI	[redacted]	[redacted]	[redacted]
p-value[‡]	<0.001	<0.001	<0.001
Outcome for patients without SVR12, n/N (%)			
Total	15/90 (16.7)	4/87 (4.6)	13/90 (14.4)
Overall virologic failure	11/90 (12.2)	3/87 (3.4)	8/90 (8.9)
Relapse[§]	11/90 (12.2)	2/85 (2.4)	7/88 (8.0)
On-treatment failure	0	1/87 (1.1)	1/90 (1.1)
Other[¶]	4/90 (4.4)	2/87 (2.3)	5/90 (5.6)

CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.
LLOQ=15 IU/mL. [redacted]; ‡ compared with pre-specified rate of spontaneous clearance of 1%; § Denominator for relapse is the number of patients who had HCV RNA <LLOQ on their last observed on-treatment HCV RNA measurement; ¶ patients who did not achieve SVR12 and did not meet virologic failure criteria.

Table 51: Summary of SVR12 rates by HCV genotype in ASTRAL-4 (FAS)

Response	SOF/VEL 12 weeks N=90	SOF/VEL+RBV 12 weeks N=87	SOF/VEL 24 weeks N=90
HCV RNA<LLOQ at week 12 post-treatment (SVR12)			
GT1			
n/N (%)	60/68 (88.2)	65/68 (95.6)	65/71 (91.5)
95% CI	[redacted]	[redacted]	[redacted]
GT1a			
n/N (%)	44/50 (88.0)	51/54 (94.4)	51/55 (92.7)
95% CI	[redacted]	[redacted]	[redacted]
GT1b			
n/N (%)	16/18 (88.9)	14/14 (100.0)	14/16 (87.5)
95% CI	[redacted]	[redacted]	[redacted]
GT2			
n/N (%)	4/4 (100.0)	4/4 (100.0)	3/4 (75.0)
95% CI	[redacted]	[redacted]	[redacted]
GT3			
n/N (%)	7/14 (50.0)	11/13 (84.6)	6/12 (50.0)
95% CI	[redacted]	[redacted]	[redacted]
GT4			
n/N (%)	4/4 (100.0)	2/2 (100.0)	2/2 (100.0)
95% CI	[redacted]	[redacted]	[redacted]
GT6			
n/N (%)	0	0	1/1 (100.0)
95% CI	-	-	[redacted]

CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.
LLOQ=15 IU/mL.

4.11.7.2 Secondary efficacy outcomes

Proportion of patients with SVR at 4 and 24 weeks

[redacted]

Analysis of SVR24 rates is planned but are not currently available in the interim clinical study report (CSR).

Proportion of patients with HCV RNA <LLOQ on treatment

A summary of the proportion of patients with HCV RNA <LLOQ on treatment at weeks 2, 4, 6, and 8 for the overall trial population (all genotypes) is presented in Table 28. There [redacted]

[redacted]

HCV change from baseline

[redacted]

Proportion of patients with virologic failure

Among the 267 patients who received at least one dose of study treatment across the three treatment groups, 22 (8.2%) experienced virologic failure; 20 relapsed and two had on-treatment virologic breakthrough (both with HCV GT3 infection) (Table 28).

- SOF/VEL 12 weeks: 11/90 (12.2%) with relapse
- SOF/VEL+RBV 12 weeks: 2/85 (2.4%) with relapse, 1/87 (1.1%) with on-treatment breakthrough
- SOF/VEL 24 weeks: 7/88 (8.0%) with relapse, 1/90 (1.1%) with on-treatment breakthrough

Eleven additional patients were classified as not having achieved SVR12:

- SOF/VEL 12 weeks: 3/90 (3.3%) died, 1/90 (1.1%) was lost to follow up
- SOF/VEL+RBV 12 weeks: 2/87 (2.3%) died
- SOF/VEL 24 weeks: 2/90 (2.2%) died, 3/90 (3.3%) were lost to follow up

Development of resistance

In this study, 255 patients had pre-treatment NS5A sequencing data available. Of these patients, 72 (28.2%) had pre-treatment NS5A resistance-associated variants and 64 (89%) achieved SVR12. By comparison, 169 of 183 patients (92.3%) who did not have pre-treatment NS5A resistance-associated variants achieved SVR12.

Among patients with HCV GT1 in the SOF/VEL+RBV 12 week group, the SVR12 rate in those with NS5A resistance-associated variants was 100%, and the rate without such variants was 98%. Among patients with HCV GT1 in both SOF/VEL groups who had pre-treatment resistance-associated variants, the SVR12 rate was 80% in the 12-week treatment group and 90% in the 24-week group; among those who did not have resistance-associated variants, the rates were 96% and 98%, respectively. Analysis in the next largest group, by genotype (CHC GT3) was limited by the small number (n=6) with resistance-associated variants.

The majority of patients who had virologic failure had NS5A resistance-associated variants at the time of failure; NS5B resistance-associated variants were less common and typically observed at low levels.

Of 251 patients for whom pre-treatment NS5B deep-sequencing data were available, eight had pre-treatment resistance-associated variants. All eight patients achieved SVR12.

Changes in liver function: CPT and MELD scores

CPT and MELD scores were available at post-treatment week 12 for 250 out of 267 patients. Of these:

- 117 (47%) had an improvement in their CPT score versus baseline
- 106 (42%) had no change
- 27 (11%) had a worsening in the CPT score (Figure 13)

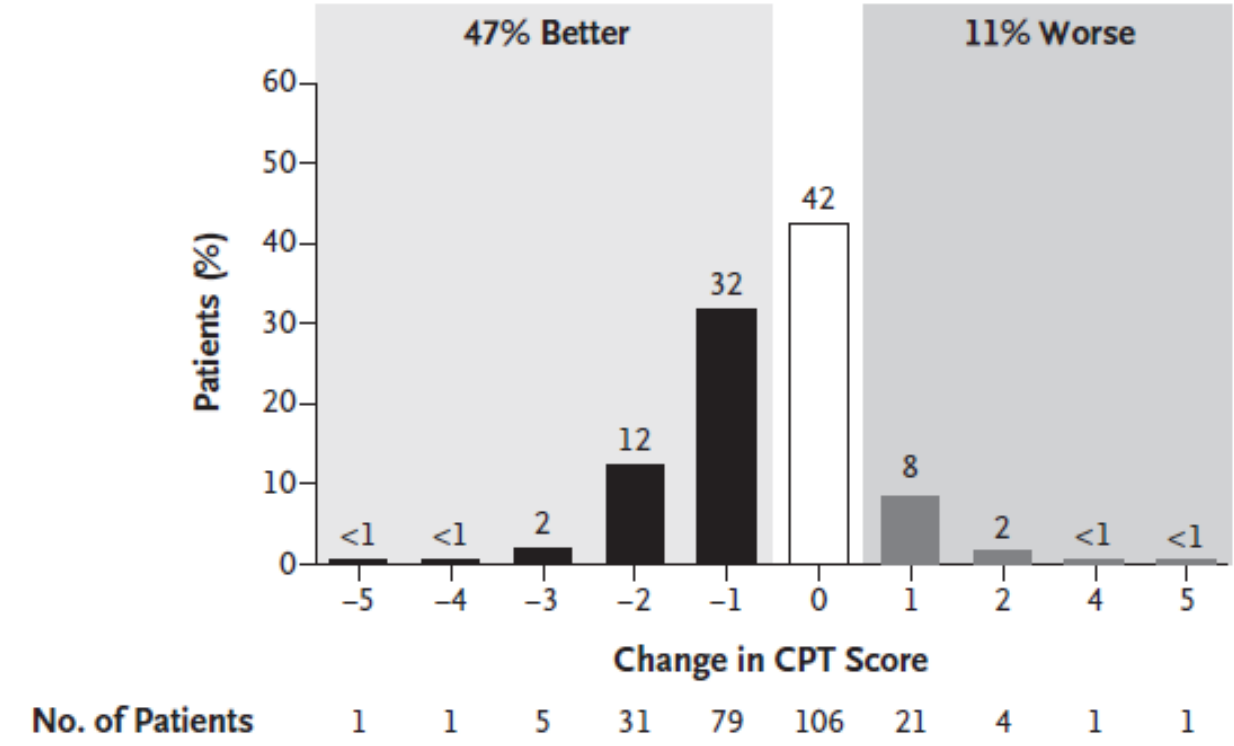
Of the 250 patients with post-treatment MELD scores, 223 patients had a baseline score <15 and 27 had a baseline score ≥15 (representing more advanced liver disease). Of those with baseline score <15 (Figure 14, panel A):

- 114 (51%) had an improved MELD score
- 49 (22%) had no change
- 60 (27%) had a worsening in the MELD score

Of those with a baseline MELD score of ≥15 (Figure 14, panel B):

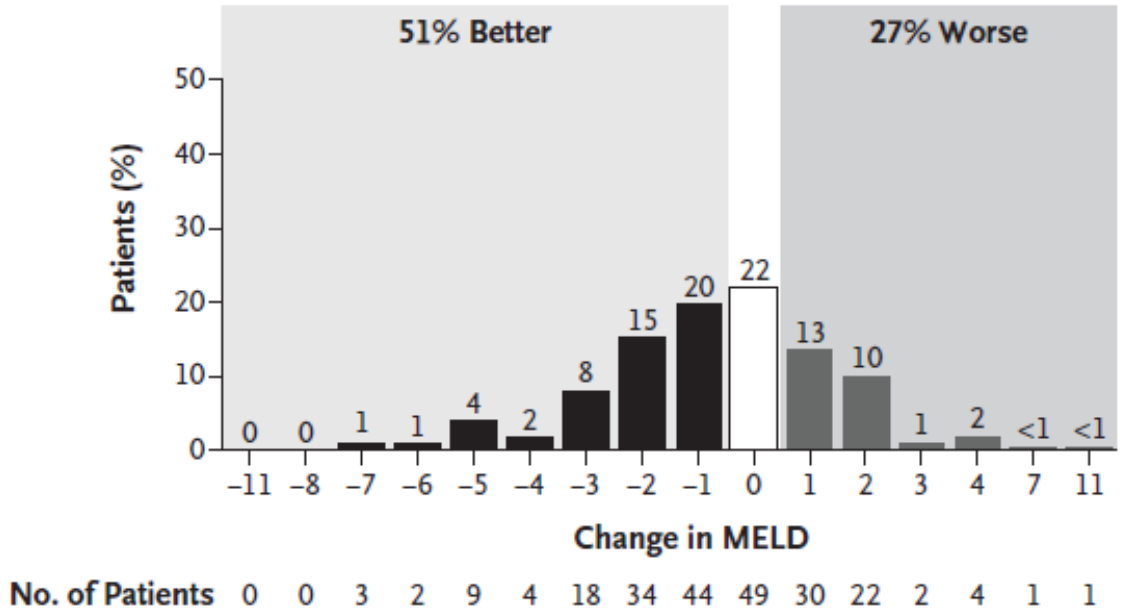
- 22 (81%) had an improved MELD score
- 3 (11%) had no change
- 2 (7%) had a worsening in the MELD score

Figure 13: Change in CPT score from baseline to post-treatment week 12

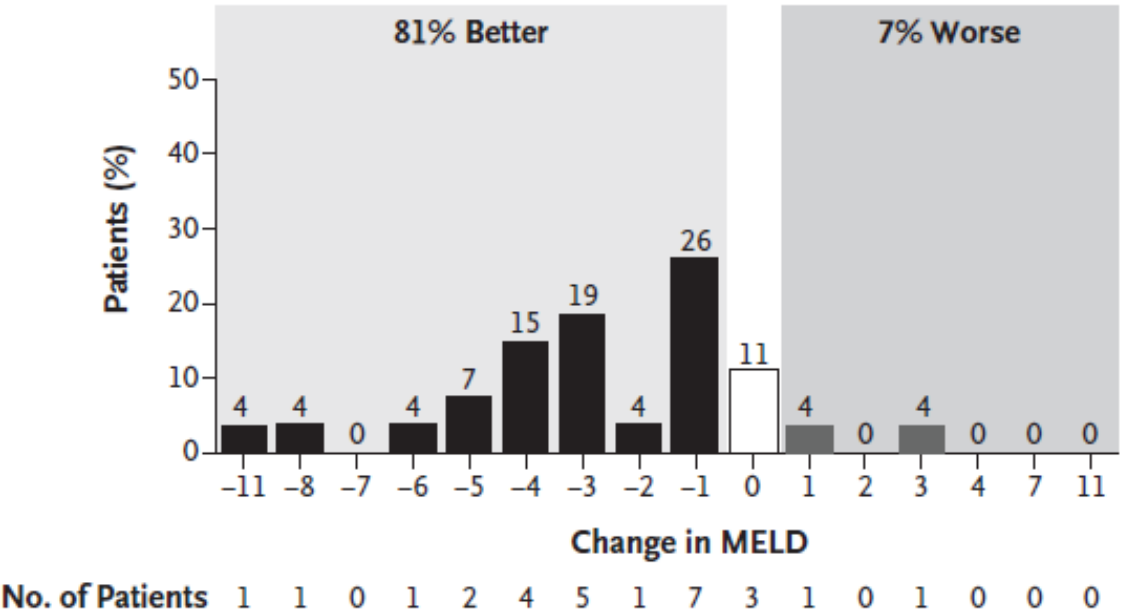


CPT scores range from 5 to 15, with higher values indicating more advanced liver disease. Data was combined for all three treatment groups. Seventeen patients who did not undergo CPT or MELD assessments at post-treatment week 12 were excluded from the analysis. Percentages may not sum to totals in subgroups because of rounding.

Figure 14: Change in MELD score from baseline to post-treatment week 12 for patients with baseline score <15 and ≥15
Panel A



Panel B



MELD scores range from 6 to 40, with higher values indicating more advanced liver disease. Data was combined for all three treatment groups. Baseline MELD score was <15 for 223 patients ≥15 for 27 patients. Columns indicate the percentage of patients categorised according to the extent of change from baseline. Seventeen patients who did not undergo CPT or MELD assessments at post-treatment week 12 were excluded from the analysis. Percentages may not sum to totals in subgroups because of rounding.

4.11.7.3 Other outcomes of interest

ALT normalisation

[redacted]

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 whether they had achieved SVR or not. These HRQL results should be interpreted with caution as multiple endpoints were tested and the study was not powered to test these exploratory endpoints.

Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C quality of life questionnaires generally indicated that there were no on-treatment decrements in HRQL in patients in either SOF/VEL group (12 or 24 weeks treatment). In the SOF/VEL+RBV 12 week group, on-treatment decreases (worsening) from baseline were generally observed in 4 of 8 domain scores of the SF-36 (domains of vitality, social functioning, role emotional, and mental health) and the mental component score. Both increases (improvement) and decreases (worsening) from baseline were observed for the domains of physical functioning, role physical, and bodily pain. The mean scores for most scales improved from EOT to post-treatment week 4 and 12 weeks.

Conclusion (ASTRAL-4)

- SOF/VEL+/-RBV for 12 weeks and SOF/VEL for 24 weeks resulted in high SVR12 rates in adult patients with chronic HCV infection and decompensated cirrhosis (CPT class B)
- The SVR12 rate was highest with SOF/VEL+RBV for 12 weeks (licensed regimen in decompensated patients): 94.3% [redacted]
- SVR12 rates were high irrespective of HCV genotype (SOF/VEL+RBV 12 weeks: GT1, 95.6%; GT2, 100.0%; GT3, 84.6%; GT4, 100%). Rates in GT2 and GT4 are limited by small patient numbers

4.11.8 *Additional data - ASTRAL-5*

ASTRAL-5 is an ongoing, open-label, single-arm, multicentre, Phase III study evaluating the safety and efficacy of SOF/VEL in patients co-infected with HCV and HIV-1. Preliminary results for this study were presented at EASL 2016 in April 2016 (158) and are provided here.

Patients were eligible if they were co-infected with HIV and HCV, had HCV GT1–6, were treatment-naïve or experienced, and were on stable ART for ≥8 weeks with CD4 cell count ≥100 cells/mm^3 and had HIV RNA ≤50 copies/mL. Up to 30% of patients could have compensated cirrhosis. Eligible ARTs were non-nucleoside reverse-transcriptase inhibitors, integrase inhibitors, and PI regimens combined with a backbone of either tenofovir disoproxil fumarate/emtricitabine or abacavir/lamivudine. All patients (n=106) were treated with SOF/VEL and baseline characteristics are presented in Table 52.

Table 52: Characteristics of participants in ASTRAL-5

Characteristic	SOF/VEL (n=106)
Age, mean years (range)	54 (25–72)
Male, n (%)	91 (86)
Black, n (%)	48 (45)
BMI, mean kg/m^2 (range)	27 (19–43)
Cirrhosis, n (%)	19 (18)
Treatment experienced, n (%)	31 (29)
IL28B CC, n (%)	24 (23)
HCV RNA, mean log_{10} IU/mL (range)	6.3 (5.0–7.4)
HCV genotype	
1a	66 (62)
1b	12 (11)
2	11 (10)
3	12 (11)
4	5 (5)
CD4 cell count, mean cells/µL (range)	598 (183–1,513)
NRTI backbone	
TDF-based with boosted agent (RTV or COBI)	56 (53)
TDF-based without boosted agent	35 (33)
ABC/3TC-based	15 (14)

Characteristic	SOF/VEL (n=106)
ART use at baseline	
PI (DRV, LPV or ATV)	50 (47)
NNRTI (RPV)	13 (12)
Integrase inhibitor (RAL or EVG)	36 (34)
Other (>1 of the above classes)	7 (7)

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; BMI, body mass index; COBI, cobicistat; DRV, darunavir; EVG, elvitegravir; HCV, hepatitis C virus; LPV, lopinavir; NRTI, nucleoside-analog reverse-transcriptase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir; RNA, ribonucleic acid; RPV, rilpivirine; RTV, ritonavir; SOF, sofosbuvir; TDF, tenofovir disoproxil fumarate; VEL, velpatasvir.

Preliminary results for ASTRAL-5 show that 95% of patients achieved both SVR4 (101 of 106) and SVR12 (99 of 104). Of the five patients who did not achieve SVR12, two relapsed, two were lost to follow-up, and one withdrew consent. Results for SVR12 when stratified by subgroup were as follows:

- Genotype:
    - GT1a, 95% (62/65);
    - GT1b, 92% (11/12);
    - GT2, 100% (11/11);
    - GT3, 92% (11/12);
    - GT4, 100% (4/4).
- Cirrhosis status:
    - Without cirrhosis, 94% (80/85);
    - With cirrhosis, 100% (19/19).
- Treatment history:
    - Treatment-naive, 93% (71/75);
    - Treatment-experienced, 97% (28/29).

Treatment with SOF/VEL for 12 weeks was safe and well tolerated with ART, including TDF-based with boosted regimens, and resulted in an overall SVR12 rate of 95%. The presence of NS5A RAVs did not impact SVR12. This preliminary data shows that SOF/VEL for 12 weeks provides a simple, safe, and highly effective treatment for patients co-infected with HIV-1 and HCV.

4.12 *Adverse reactions*

4.12.1 *Studies reported in section 4.2*

Safety evidence for SOF/VEL in support of this technology appraisal is drawn from the four ASTRAL trials, the methodologies for which have been described previously in Section 4.3 (ASTRAL-1, -2 and -3) and Section 4.10.9.1 (ASTRAL-4). These four studies form the basis of the safety assessment submitted to the EMA for marketing authorisation and subsequently presented in the draft SmPC (SmPC section 4.8).

4.12.1.1 ASTRAL-3

In ASTRAL-3, a lower percentage of patients in the SOF/VEL 12 week group experienced any AE (n=245; 88%) compared with SOF+RBV for 24 weeks (n=260; 95%), predominately due to a higher percentage of AEs known to be associated with RBV: fatigue (26% vs 38%), insomnia (11% vs 27%), nausea (17% vs 21%), irritability (8% vs 15%), cough (5% vs 13%), pruritus (3% vs 13%), and dyspepsia (3% vs 11%) (Table 53).

AE severity

[redacted]

Treatment-related AEs

[redacted]

SAEs and deaths

SAEs were reported in six (2%) patients in the SOF/VEL group versus 15 (5%) patients in the SOF+RBV group. No SAEs were reported in more than one patient, [redacted]

In total, there were three deaths reported, all of which occurred in the SOF+RBV group (one due to natural causes, one from gunshot wounds, and one from unknown causes).

Discontinuations

In total, nine patients prematurely discontinued due to study drug, all of which were in the SOF+RBV group. [redacted]

Other AEs

Among patients in the SOF+RBV group, 10 (4%) had decreased haemoglobin values (<10 g/dL) versus no patients in the SOF/VEL group. Grade 3 or 4 hyperbilirubinaemia – a known side effect of treatment with RBV – was seen in three patients receiving treatment with SOF+RBV. No Grade 3 or 4 elevations in bilirubin were observed in the SOF/VEL group.

Table 53: ASTRAL-3 adverse events summary

Adverse events, n (%)	SOF/VEL 12 week (N=277)	SOF+RBV 24 week (N=275)	Relative risk (95% CI)
≥1 AE	245 (88.4)	260 (94.5)	0.94 (0.89, 0.98)
≥1 treatment-related AE	[redacted]	[redacted]	0.78 (0.70, 0.88)
Grade 3 or 4 AE	[redacted]	[redacted]	0.52 (0.26, 1.02)
Grade 3 AE	[redacted]	[redacted]	0.60 (0.30, 1.19)
Grade 4 AE	[redacted]	[redacted]	0.14 (0.01, 2.73)
Grade 3/4 AEs in >1 patient			
Headache	[redacted]	[redacted]	0.20 (0.01, 4.12)
Abdominal pain	[redacted]	[redacted]	0.20 (0.01, 4.12)
Anxiety	[redacted]	[redacted]	0.20 (0.01, 4.12)
≥1 SAE	6 (2.2)	15 (5.5)	0.40 (0.16, 1.01)
≥1 treatment-related SAE	[redacted]	[redacted]	0.33 (0.01, 8.09)
Deaths	0	3 (1.1)	0.14 (0.01, 2.73)
Discontinuation due to AEs	0	9 (3.3)	0.05 (0.00, 0.89)
Common AEs[†]			
Headache	90 (32.5)	89 (32.4)	1.00 (0.79, 1.28)
Fatigue	71 (25.6)	105 (38.2)	0.67 (0.52, 0.86)
Insomnia	31 (11.2)	74 (26.9)	0.42 (0.28, 0.61)
Nausea	46 (16.6)	58 (21.1)	0.79 (0.56, 1.12)
Nasopharyngitis	34 (12.3)	33 (12.0)	1.02 (0.65, 1.60)
Irritability	23 (8.3)	40 (14.5)	0.57 (0.35, 0.93)
Cough	14 (5.1)	35 (12.7)	0.40 (0.22, 0.72)
Pruritus	8 (2.9)	35 (12.7)	0.23 (0.11, 0.48)
Dyspepsia	9 (3.2)	30 (10.9)	0.30 (0.14, 0.62)
Back pain	[redacted]	[redacted]	1.24 (0.71, 2.18)
Asthenia	[redacted]	[redacted]	0.61 (0.34, 1.11)
Diarrhoea	[redacted]	[redacted]	0.95 (0.52, 1.70)
Dizziness	[redacted]	[redacted]	0.71 (0.37, 1.35)
Constipation	[redacted]	[redacted]	0.61 (0.31, 1.20)
Arthralgia	[redacted]	[redacted]	0.45 (0.22, 0.94)
Dyspnoea	[redacted]	[redacted]	0.36 (0.16, 0.80)
Abdominal pain	[redacted]	[redacted]	0.52 (0.25, 1.10)
Muscle spasms	[redacted]	[redacted]	0.81 (0.40, 1.64)
Rash	[redacted]	[redacted]	1.06 (0.52, 2.16)
Anxiety	[redacted]	[redacted]	0.33 (0.14, 0.77)

Adverse events, n (%)	SOF/VEL 12 week (N=277)	SOF+RBV 24 week (N=275)	Relative risk (95% CI)
Vomiting	[redacted]	[redacted]	0.40 (0.18, 0.89)
Dry skin	[redacted]	[redacted]	0.08 (0.02, 0.33)
Anaemia	[redacted]	[redacted]	0.04 (0.01, 0.30)
Myalgia	[redacted]	[redacted]	0.66 (0.30, 1.45)
Sleep disorder	[redacted]	[redacted]	0.60 (0.27, 1.34)
Dyspnoea exertional	[redacted]	[redacted]	0.15 (0.04, 0.50)
Decreased appetite	[redacted]	[redacted]	0.57 (0.24, 1.33)
Disturbance in attention	[redacted]	[redacted]	0.50 (0.20, 1.21)
Pyrexia	[redacted]	[redacted]	0.28 (0.09, 0.85)

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

4.12.1.2 ASTRAL-2

In ASTRAL-2, a smaller percentage of patients in the SOF/VEL 12 week group experienced any AE compared with the SOF+RBV 12 week group (69% vs 77%, respectively). This was largely due to higher rates of AEs typically associated with RBV such as fatigue (15% vs 36%), headache (18% vs 22%), nausea (10% vs 14%) and insomnia (4% vs 14%) (Table 54).

AE severity

[redacted]

Treatment-related AEs

[redacted]

SAEs and deaths

SAEs were reported in two (1.5%) patients in each group, respectively. No SAEs were reported in more than one patient[redacted]

There were two deaths reported, both in the SOF/VEL group, during the post-treatment follow-up (one due to cardiac arrest and one due to complications related to metastatic lung cancer).

Discontinuations

One patient prematurely discontinued study drug due to an AE in the SOF/VEL group (difficulty concentrating, headache and anxiety[redacted]

Other AEs

Among patients in the SOF+RBV group, six (5%) had decreased haemoglobin values (<10 g/dL) versus no patients in the SOF/VEL group. Grade 3 hyperbilirubinaemia – a known side effect of treatment with RBV – was seen in three patients receiving SOF+RBV. No Grade 3 or 4 elevations in bilirubin were observed in the SOF/VEL group.

Table 54: ASTRAL-2 adverse events summary

Adverse events, n (%)	SOF/VEL 12 week (N=134)	SOF+RBV 12 week (N=132)	Relative risk (95% CI)
≥1 AE	92 (68.7)	101 (76.5)	0.90 (0.77, 1.04)
≥1 treatment-related AE	[redacted]	[redacted]	0.59 (0.45, 0.78)
Grade 3 or 4 AE	[redacted]	[redacted]	0.99 (0.20, 4.79)
Grade 3 AE	[redacted]	[redacted]	0.99 (0.20, 4.79)
Grade 4 AE	[redacted]	[redacted]	-
Grade 3/4 AEs in >1 patient			
Anxiety	[redacted]	[redacted]	4.93 (0.24, 101.64)
≥1 SAE	2 (1.5)	2 (1.5)	0.99 (0.14, 6.89)
≥1 treatment-related SAE	[redacted]	[redacted]	-
Deaths	2 (1.5)	0	4.93 (0.24, 101.64)
Discontinuation due to AEs	1 (0.7)	0	2.96 (0.12, 71.91)
Common AEs[†]			
Fatigue	20 (14.9)	47 (35.6)	0.42 (0.26, 0.67)
Headache	24 (17.9)	29 (22.0)	0.82 (0.50, 1.32)
Nausea	14 (10.4)	19 (14.4)	0.73 (0.38, 1.39)
Insomnia	6 (4.5)	18 (13.6)	0.33 (0.13, 0.80)
Anxiety	[redacted]	[redacted]	0.99 (0.38, 2.55)
Arthralgia	[redacted]	[redacted]	0.74 (0.26, 2.07)
Irritability	4 (3.0)	9 (6.8)	0.44 (0.14, 1.39)
Pruritus	6 (4.5)	7 (5.3)	0.84 (0.29, 2.45)
Upper respiratory tract infection	[redacted]	[redacted]	1.58 (0.53, 4.69)
Vomiting	[redacted]	[redacted]	0.62 (0.21, 1.83)
Abdominal pain	[redacted]	[redacted]	0.70 (0.23, 2.16)
Sinusitis	[redacted]	[redacted]	1.38 (0.45, 4.24)
Dizziness	[redacted]	[redacted]	0.37 (0.10, 1.36)
Nasopharyngitis	8 (6.0)	2 (1.5)	3.94 (0.85, 18.21)
Back pain	[redacted]	[redacted]	0.28 (0.06, 1.33)
Rash	[redacted]	[redacted]	0.28 (0.06, 1.33)
Anaemia	[redacted]	[redacted]	0.06 (0.00, 0.99)

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

4.12.1.3 ASTRAL-1

Overall, SOF/VEL for 12 weeks was well tolerated with patients experiencing similar type, incidence, and severity of AEs as patients in the placebo 12 week group.

Incidence rates in the SOF/VEL and placebo groups of any AE (485 [78%] vs 89 [77%] patients, respectively), and of the most common individual AEs, were generally comparable (Table 55). The most common AEs were headache, fatigue, nausea and nasopharyngitis.

AE severity

[redacted]

Treatment-related AEs

[redacted]

SAEs and deaths

SAEs were reported in 15 (2%) patients in the SOF/VEL group. There were no SAEs in the placebo group. No SAEs were reported in more than one patient, [redacted]

One patient in the SOF/VEL group died eight days after the end of treatment (cause of death was not determined).

Discontinuations

One (<1%) patient in the SOF/VEL group discontinued treatment prematurely because of an AE (anxiety attack). In the placebo group, two (2%) patients discontinued treatment because of an elevated aminotransferase level, a pre-specified criterion for discontinuation.

Other AEs

Among patients in the SOF/VEL group, two (<1%) had decreased haemoglobin values (<10 g/dL) versus no patients in the placebo group.

Table 55: ASTRAL-1 adverse events summary

Adverse events, n (%)	SOF/VEL 12 week (N=624)	Placebo (N=116)	Relative risk (95% CI)
≥1 AE	485 (77.7)	89 (76.7)	1.01 (0.91, 1.13)
≥1 treatment-related AE	[redacted]	[redacted]	1.09 (0.88, 1.35)
Grade 3 or 4 AE	[redacted]	[redacted]	3.35 (0.45, 24.82)

Adverse events, n (%)	SOF/VEL 12 week (N=624)	Placebo (N=116)	Relative risk (95% CI)
Grade 3 AE	[redacted]	[redacted]	2.97 (0.40, 22.21)
Grade 4 AE	[redacted]	[redacted]	0.94 (0.05, 19.37)
Grade 3/4 AEs in >1 patient			
Headache	[redacted]	[redacted]	1.31 (0.07, 25.20)
≥1 SAE	15 (2.4)	0	5.80 (0.35, 96.32)
≥1 treatment-related SAE	[redacted]	[redacted]	-
Deaths	1 (0.2)	0	0.56 (0.02, 13.70)
Discontinuation due to AEs	1 (0.2)	2 (1.7)	0.09 (0.01, 1.02)
Common AEs†			
Headache	182 (29.2)	33 (28.4)	1.03 (0.75, 1.40)
Fatigue	126 (20.2)	23 (19.8)	1.02 (0.68, 1.52)
Nasopharyngitis	79 (12.7)	12 (10.3)	1.22 (0.69, 2.17)
Nausea	75 (12.0)	13 (11.2)	1.07 (0.62, 1.87)
Insomnia	50 (8.0)	11 (9.5)	0.84 (0.45, 1.57)
Diarrhoea	48 (7.7)	8 (6.9)	1.12 (0.54, 2.30)
Asthenia	41 (6.6)	9 (7.8)	0.85 (0.42, 1.69)
Arthralgia	40 (6.4)	9 (7.8)	0.83 (0.41, 1.66)
Cough	39 (6.3)	4 (3.4)	1.81 (0.66, 4.98)
Back pain	29 (4.6)	11 (9.5)	0.49 (0.25, 0.95)
Myalgia	25 (4.0)	6 (5.2)	0.77 (0.32, 1.85)

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

4.12.1.4 ASTRAL-4

In ASTRAL-4, a lower percentage of patients in the SOF/VEL groups experienced any AE (n=73, 81% for both the 12 and 24 week groups) compared with the SOF/VEL+RBV group (n=79, 91%). Of the most common AEs fewer patients in the SOF/VEL 12 and 24 week groups compared with the SOF/VEL+RBV group experienced fatigue (26% and 23% vs 39%), anaemia (4% and 3% vs 31%), diarrhoea (7% and 8% vs 21%), insomnia (10% and 10% vs 14%), muscle spasm (3% and 4% vs 11%), dyspnoea (4% and 2% vs 10%) and cough (2% and 0 vs 10%) (Table 56).

AE severity

[redacted]

[redacted]

Treatment-related AEs

[redacted]

SAEs and deaths

The incidence of SAEs was similar between the treatment groups, with 17 (19%) and 16 (18%) patients experiencing any SAE in the SOF/VEL 12 and 24 week groups, compared with 14 (16%) patients in the SOF/VEL+RBV group. The most common SAEs were hepatic encephalopathy and sepsis with each event occurring in five patients across the three treatment groups.

Nine deaths occurred during the study, three in each treatment group. None of the deaths were considered to be treatment-related. Complications of end-stage liver disease were the most common cause of death.

Discontinuations

One (<1%) patient in the SOF/VEL 12 week group discontinued treatment prematurely, compared with four (5%) and four (4%) patients in the SOF/VEL+RBV and SOF/VEL 24 week groups. [redacted]

No AE that led to discontinuation of a study drug was reported in more than one patient.

Other AEs

Decreased haemoglobin values (<10 g/dL) were observed in seven (8%) and eight (9%) patients in the SOF/VEL 12 and 24 week groups, respectively, compared with 20 (23%) patients in the SOF/VEL+RBV group.

Table 56: ASTRAL-4 adverse events summary

Adverse events, n (%)	SOF/VEL 12 week (N=90)	SOF/VEL+RBV 12 week (N=87)	SOF/VEL 24 week (N=90)	Relative risk (SOF/VEL+RBV vs SOF/VEL 12) (95% CI)	Relative risk (SOF/VEL+RBV vs SOF/VEL 24) (95% CI)
≥1 AE	73 (81.1)	79 (90.8)	73 (81.1)	1.12 (0.99, 1.26)	1.12 (0.99, 1.26)
≥1 treatment-related AE	[redacted]	[redacted]	[redacted]	1.38 (1.07, 1.77)	1.83 (1.35, 2.46)
Grade 3 or 4 AE	[redacted]	[redacted]	[redacted]	0.71 (0.35, 1.44)	0.67 (0.33, 1.35)
Grade 3 AE	[redacted]	[redacted]	[redacted]	0.74 (0.35, 1.57)	0.69 (0.33, 1.45)
Grade 4 AE	[redacted]	[redacted]	[redacted]	0.52 (0.05, 5.60)	0.52 (0.05, 5.60)
Grade 3/4 AEs in >1 patient					
Sepsis	[redacted]	[redacted]	[redacted]	3.10 (0.33, 29.27)	3.10 (0.33, 29.27)

Adverse events, n (%)	SOF/VEL 12 week (N=90)	SOF/VEL+RBV 12 week (N=87)	SOF/VEL 24 week (N=90)	Relative risk (SOF/VEL+RBV vs SOF/VEL 12) (95% CI)	Relative risk (SOF/VEL+RBV vs SOF/VEL 24) (95% CI)
Gastrointestinal haemorrhage	[redacted]	[redacted]	[redacted]	0.15 (0.01, 2.82)	1.03 (0.02, 51.55)
Hepatocellular carcinoma	[redacted]	[redacted]	[redacted]	-	0.15 (0.01, 2.82)
Hyponatraemia	[redacted]	[redacted]	[redacted]	2.07 (0.19, 22.41)	5.17 (0.25, 106.19)
Asthenia	[redacted]	[redacted]	[redacted]	5.17 (0.25, 106.19)	5.17 (0.25, 106.19)
Peritonitis bacterial	[redacted]	[redacted]	[redacted]	5.17 (0.25, 106.19)	5.17 (0.25, 106.19)
≥1 SAE	17 (18.9)	14 (16.1)	16 (17.8)	0.85 (0.45, 1.62)	0.91 (0.47, 1.74)
≥1 treatment-related SAE	[redacted]	[redacted]	[redacted]	3.10 (0.13, 75.14)	1.03 (0.07, 16.28)
Deaths	3 (3.3)	3 (3.4)	3 (3.3)	1.03 (0.21, 4.99)	1.03 (0.21, 4.99)
Discontinuation due to AEs	1 (1.1)	4 (4.6)	4 (4.4)	4.14 (0.47, 36.29)	1.03 (0.27, 4.01)
Common AEs†					
Fatigue	23 (25.6)	34 (39.1)	21 (23.3)	1.53 (0.99, 2.37)	1.67 (1.06, 2.65)
Nausea	22 (24.4)	22 (25.3)	18 (20.0)	1.03 (0.62, 1.73)	1.26 (0.73, 2.19)
Headache	23 (25.6)	18 (20.7)	17 (18.9)	0.81 (0.47, 1.39)	1.10 (0.60, 1.98)
Anaemia	4 (4.4)	27 (31.0)	3 (3.3)	6.98 (2.55, 19.13)	9.31 (2.93, 29.58)
Diarrhoea	6 (6.7)	18 (20.7)	7 (7.8)	3.10 (1.29, 7.45)	2.66 (1.17, 6.05)
Insomnia	9 (10.0)	12 (13.8)	9 (10.0)	1.38 (0.61, 3.11)	1.38 (0.61, 3.11)
Pruritus	10 (11.1)	4 (4.6)	4 (4.4)	0.41 (0.13, 1.27)	1.03 (0.27, 4.01)
Muscle spasms	3 (3.3)	10 (11.5)	4 (4.4)	3.45 (0.98, 12.11)	2.59 (0.84, 7.94)
Dyspnoea	4 (4.4)	9 (10.3)	2 (2.2)	2.33 (0.74, 7.28)	4.66 (1.03, 20.94)
Cough	2 (2.2)	9 (10.3)	0	4.66 (1.03, 20.94)	19.65 (1.16, 332.52)

AE, adverse event; CI, confidence interval; SAE, serious adverse event.
†Common AEs were those that occurred in ≥10% of patients in any treatment group.

4.12.2 *Additional studies*

Not applicable.

4.12.3 *Safety overview*

Patients with or without compensated cirrhosis

The safety assessment of SOF/VEL provided to the EMA for marketing authorisation and presented in the draft SmPC was based on data pooled from ASTRAL-1, -2 and -3 from patients with HCV GT1–6 infection (with or without compensated cirrhosis) which included data from:

- 1,035 patients who received SOF/VEL for 12 weeks

- 116 patients who received placebo for 12 weeks
- 132 patients who received SOF+RBV for 12 weeks
- 275 patients who received SOF+RBV for 24 weeks.

This analysis showed that only 0.2% of patients receiving SOF/VEL for 12 weeks permanently discontinued treatment due to AEs. No adverse drug reactions specific to SOF/VEL were identified, with the type, incidence and severity of AEs being comparable to placebo. Across these three ASTRAL trials, headache, fatigue, nausea and nasopharyngitis were the most common (incidence ≥ 10%) treatment emergent AEs reported in patients treated with SOF/VEL for 12 weeks.

AEs were generally mild or moderate in severity with only 3.2% of patients experiencing any Grade 3 or Grade 4 AE. Headache (0.5%) and anxiety (0.3%) were the only Grade 3 AEs that occurred in more than two patients. Two patients (0.2%) had Grade 4 AEs (malignant lung neoplasm and one patient who died in his sleep), both of which were considered unrelated to study drug.

By comparison Grade 3 AEs occurred at similar rates in the placebo and SOF+RBV 12 week groups compared with the SOF/VEL 12 week group, while higher rates were observed in the SOF+RBV 24 week group likely due to cumulative RBV toxicity. There were no Grade 4 events in the placebo and SOF+RBV 12 week groups, while three patients (1.1%) experienced Grade 4 AEs in the SOF+RBV 24 week group.

Patients with decompensated cirrhosis

In patients with decompensated cirrhosis (CPT class B cirrhosis) no adverse drug reactions specific to SOF/VEL were identified following treatment with SOF/VEL for 12 weeks (n=90), SOF/VEL+RBV for 12 weeks (n=87) or SOF/VEL for 24 weeks (n=90). The AEs observed were consistent with the expected clinical sequelae of decompensated liver disease, or the known toxicity profile of RBV for patients receiving SOF/VEL in combination with RBV.

Among the 87 patients who were treated with SOF/VEL+RBV for 12 weeks, decreases in haemoglobin to less than 10 mg/dL during treatment were experienced by 23% patients, respectively. RBV was discontinued in 15% of patients treated with SOF/VEL+RBV for 12 weeks due to AEs.

4.13 *Interpretation of clinical effectiveness and safety evidence*

4.13.1 *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 for patients with CHC infection of any genotype (GT1–6) are summarised in Table 57 and described below, with genotype specific summaries provided later in this section.

Very high cure rates (SVR12) of 89–100% can be achieved in adult patients with CHC GT1–6 infection with SOF/VEL administered as an STR once daily for 12 weeks. In ASTRAL-2 and ASTRAL-3, SVR12 rates were significantly superior to the active comparator SOF+RBV (12 weeks, ASTRAL-2; 24 weeks, ASTRAL-3). In ASTRAL-1 SVR12 was significantly superior to the pre-defined performance goal of 85%.

High cure rates were achieved irrespective of cirrhotic status (without cirrhosis or with compensated cirrhosis) or prior CHC treatment experience (treatment-naïve or treatment-experienced). These are characteristics which historically have been linked with poor response to IFN-containing regimens (27), and which, in the current era of DAAs still limit the effectiveness of some treatment regimens, including SOF+RBV (28).

Furthermore, some patients 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 3.3), SOF/VEL provides an IFN-free and RBV-free treatment option that is highly effective across all genotypes.

In particular, SOF/VEL is a treatment option that fulfils a very significant unmet clinical need for GT3 patients. This is a difficult-to-treat patient group which accounts for 44% of the CHC population in England (3), but which remains a clinical challenge despite the recent emergence of DAAs (28); GT3 infection is associated with significantly higher rates of disease progression and mortality than other genotypes (6-8). Currently Peg-IFN+RBV for 24 weeks is recommended by NICE for GT3 CHC patients, but SVR rates are poor (e.g. 63% in treatment-naïve patients including those with compensated cirrhosis (19)) and treatment with Peg-IFN+RBV is associated with significant limitations from a tolerability and monitoring perspective, that limit its utility in clinical practice (14, 18, 20).

Current NICE-recommended DAAs have varying efficacy in GT3 infection and NICE have limited their use to specific subgroups, based on prior treatment experience, cirrhotic status and IFN eligibility (see Section 3.3). SOF+RBV for 24 weeks leads to relatively poor response in treatment-experienced patients or those who have cirrhosis (63% and 66% respectively, ASTRAL-3, Section 4.8). SOF+DCV for 12 weeks is associated with a reasonable SVR rate in previously treated patients (86% ALLY-3 (150)) but response is still poor among those with compensated cirrhosis (63% ALLY-3 (150)). The addition of Peg-IFN to SOF+RBV improves SVR outcomes (91% in treatment-experienced and 88% in those with cirrhosis) but at the expense of greater toxic effects and the exclusion of patients who are ineligible for IFN (86). In this context, the finding that SVR rates are consistently high with SOF/VEL across patient subgroups, including those with cirrhosis and prior treatment failure, represents an improvement in outcome over current treatment options, along with a shorter duration of treatment in some cases and fewer side effects owing to the removal of Peg-IFN and/or RBV from the regimen.

Despite the recent NICE appraisals of DAAs, no IFN-free or RBV-free treatment is available and recommended by NICE for all patients with GT3 CHC who are treatment-naïve and without cirrhosis. Aside from having the potential to fulfil this significant unmet clinical need, the availability of a pan-genotypic, short duration, IFN- and RBV-free treatment option such as SOF/VEL creates a realistic opportunity to eliminate the burden of HCV infection in England and Wales. The value of SOF/VEL to the healthcare system in England and Wales would be even more pronounced in resource-constrained settings (e.g. prisons) where rapid genotyping of CHC patients may not be practical or reliably interpreted. For example, in cases where a patient is infected with two separate genotypes of viruses (mixed populations) or the viral genotype is a dual recombinant form, with gene portions of two separate genotypes combined within one virus. As discussed in Section 5.7.1.1, this is of particular clinical relevance in patients with GT2 CHC. Given that SOF/VEL requires no genotyping, it would potentially simplify treatment choice, enabling CHC treatment to be delivered in a greater number and variety of healthcare

settings, thereby enabling a greater number of CHC patients to be treated in England and Wales as compared to historic treatment rates.

For adult patients with more advanced liver disease (decompensated cirrhosis), the addition of RBV to the SOF/VEL treatment regimen (12 weeks treatment) also enables high cure rates (SVR12 94%) to be achieved (ASTRAL-4).

Across the ASTRAL RCTs (ASTRAL-1, -2, -3) treatment with SOF/VEL resulted in a rapid and sustained decline in HCV RNA levels, with >90% of patients achieving a virologic response below the level of quantification after 4 weeks of treatment. This response negates the need for on-treatment monitoring of HCV RNA or response-guided therapy for SOF/VEL regimens and is in contrast to other therapies, such as Peg-IFN and PI-based regimens.

Of 1,035 patients randomised to and receiving at least one dose of SOF/VEL in ASTRAL-1, -2 and -3 (FAS), 98.1% (1,015) were cured of their CHC, 1.3% (13) experienced virologic relapse after treatment, none experienced on-treatment failure and 0.7% (7) were lost to follow-up, discontinued due to AEs or died.

SOF/VEL has a high barrier to the development of treatment-resistant mutations. Deep sequencing showed that, of the 13 patients experiencing relapse, none had resistance to SOF. Twelve had NS5A mutations at relapse that could confer resistance to VEL, of which seven had NS5A mutations at study baselines. However, high SVR12 rates were achieved in the presence of baseline NS5A resistance-associated variants, observed in between 16% (ASTRAL-3) and 60% (ASTRAL-2) of the overall study populations. Thus, the presence of resistance associated variants at baseline appears to have poor predictive value for virologic failure when patients are treated with SOF/VEL.

HRQL questionnaires indicated no on-treatment decrements in HRQL in SOF/VEL treated patients. Improvements in HRQL were observed for most scales from the end of treatment to post-treatment week 4 and 12. In ASTRAL-1 improvements were generally significantly better than placebo ($p<0.05$).

The safety and tolerability data from ASTRAL-1, -2 and -3 demonstrate that SOF/VEL is well tolerated; no adverse drug reactions specific to SOF/VEL were identified with the type, incidence and severity of AEs being comparable to placebo. Similarly in patients with decompensated cirrhosis (ASTRAL-4) treated with SOF/VEL+RBV for 12 weeks no adverse drug reactions to SOF/VEL were identified, while the AEs observed were consistent with the expected clinical sequelae of decompensated liver disease, or the known toxicity profile of RBV.

Table 57: Key data supporting licensed treatment regimens for SOF/VEL (+/-RBV) 12-week regimens

Genotype	Cirrhotic status	Prior treatment	+RBV?	Study	SVR12, n/N (%)	Relapsers, n/N (%)‡§	Section
GT3	Non-cirrhotic	TN	-	ASTRAL-3	160/163 (98.2)	1/163 (0.6)¶	4.8.2
		TE	-	ASTRAL-3	31/34 (91.2)	3/34 (8.8)¶	
	Cirrhotic	TN	-	ASTRAL-3	40/43 (93.0)	3/43 (7.0)¶	
		TE	-	ASTRAL-3	33/37 (89.2)	4/37 (10.8)¶	
GT2	Non-cirrhotic	TN	-	ASTRAL-2	99/100 (99.0)	0	
		TE	-	ASTRAL-2	15/15 (100.0)	0	
		TN+TE	-	ASTRAL-1	93/93 (100.0)	0	
	Cirrhotic	TN	-	ASTRAL-2	15/15 (100.0)	0	
		TE	-	ASTRAL-2	4/4 (100.0)	0	
		TN+TE	-	ASTRAL-1	10/10 (100.0)	0	
GT1	Non-cirrhotic	TN+TE	-	ASTRAL-1	251/255 (98.4)	1/255 (0.4)	
	Cirrhotic	TN+TE	-	ASTRAL-1	72/73 (98.6)	1/73 (1.4)	
GT1a	Non-cirrhotic	TN+TE	-	ASTRAL-1	157/161 (97.5)	1/161 (0.6)	
	Cirrhotic	TN+TE	-	ASTRAL-1	49/49 (100.0)	0	
GT1b	Non-cirrhotic	TN+TE	-	ASTRAL-1	94/94 (100.0)	0	
	Cirrhotic	TN+TE	-	ASTRAL-1	23/24 (95.8)	1/24 (4.2)	
GT4	Non-cirrhotic	TN+TE	-	ASTRAL-1	89/89 (100.0)	0	
	Cirrhotic	TN+TE	-	ASTRAL-1	27/27 (100.0)	0	
GT5	Non-cirrhotic	TN+TE	-	ASTRAL-1	28/29 (96.6)	0	
	Cirrhotic	TN+TE	-	ASTRAL-1	5/5 (100.0)	0	
GT6	Non-cirrhotic	TN+TE	-	ASTRAL-1	35/35 (100.0)	0	
	Cirrhotic	TN+TE	-	ASTRAL-1	6/6 (100.0)	0	
GT1–6	Decompensated cirrhosis	TN+TE	+RBV	ASTRAL-4	82/87 (94.3)	2/87 (2.3)	4.11.7

GT, genotype; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir.
† Across all ASTRAL trials treatment-experienced patients include those who have failed prior treatment with Peg-IFN+RBV or DAA+Peg-IFN+RBV.
‡ Relapse rates include all patients in the FAS. These rates may differ on occasions from rates presented in Sections 4.7 and 4.11.7, where the denominator was the number of patients with virologic response at the end of treatment ; § Reasons for not achieving SVR12 other than relapse include lost to follow-up, treatment discontinuation due to AEs and death; ¶ Source: Mangia et al AASLD 2015 (159).

GT3 patients

- In ASTRAL-3, SOF/VEL given for 12 weeks to patients with chronic GT3 infection was superior to SOF+RBV given for 24 weeks, resulting in an SVR12 of 95.3% ($p<0.001$) compared with 80.7%
    - SOF+RBV for 24 weeks represents one of the few NICE-approved treatment options currently available to patients with chronic GT3 infection (See Section 3.3)
- SVR12 rates were consistently high (>89%), irrespective of presence or absence of cirrhosis, or prior treatment experience:
    - Treatment-naïve without cirrhosis: 98.2% SOF/VEL versus 91.0% SOF+RBV
    - Treatment-naïve with cirrhosis: 93.0% SOF/VEL versus 73.3% SOF+RBV
    - Treatment-experienced without cirrhosis: 91.2% SOF/VEL versus 71.0% SOF+RBV
    - Treatment-experienced with cirrhosis: 89.2% SOF/VEL versus 57.9% SOF+RBV

GT2 patients

- In ASTRAL-2, SOF/VEL given for 12 weeks to patients with chronic GT2 infection was superior to SOF+RBV given for 12 weeks, resulting in an SVR12 of 99.3% ($p=0.018$) compared with 93.9%
    - SOF+RBV for 12 weeks is the only NICE-approved IFN-free treatment option currently available to patients with chronic GT2 infection (See Section 3.3)
- SVR12 rates with SOF/VEL 12 weeks were consistently high (≥99%), irrespective of presence or absence of cirrhosis, or prior treatment experience
- In ASTRAL-1 SVR12 rates for the GT2 subgroup were similarly high (100%) for those treated with SOF/VEL for 12 weeks

GT1 patients

- In ASTRAL-1, SOF/VEL given for 12 weeks resulted in SVR12 rates of 98.1% in patients with chronic GT1a infection and 99.2% in those with GT1b infection, giving a rate in GT1 overall of 98.5%
- Analysis by presence/absence of cirrhosis or by prior treatment experience showed that response in patients with GT1a or GT1b infection was consistently high (≥95.8%)

GT4, GT5, GT6 patients

- In ASTRAL-1, SOF/VEL given for 12 weeks resulted in SVR12 rates of 100% in patients with chronic GT4 infection, 97.1% in those with GT5, and 100% in patients with GT6 infection
- Responses appeared to be unaffected by presence/absence of cirrhosis or by prior treatment experience with SVR12 rates being consistently high (≥95.8%). Rates in some GT5 or GT6 subgroups were limited by small numbers of patients ($n<10$)

Patients with decompensated cirrhosis

- In adult patients with chronic HCV infection and decompensated cirrhosis (CPT class B) a cure rate of 94.3% was achieved with SOF/VEL+RBV for 12 weeks (licensed regimen in decompensated patients)
- SVR12 rates with SOF/VEL+RBV 12 weeks were high irrespective of HCV genotype: GT1, 95.6%; GT2, 100.0%; GT3, 84.6%; GT4, 100%. Rates were limited by small patients numbers in those with GT3 infection (n=13) and those with GT2 or GT4 infection (n<5). There were no patients with GT6 infection in the SOF/VEL 12 week group

4.13.2 *Strengths and limitations of the clinical evidence base for the technology*

Strengths:

- The efficacy and safety of SOF/VEL regimens – SOF/VEL or SOF/VEL+RBV – at the SmPC recommended treatment duration of 12 weeks has been assessed in a comprehensive clinical trial programme, comprising:
    - Three pivotal randomised, active- or placebo-controlled, multicentre Phase III studies, ASTRAL-1, -2 and -3 in adult patients with CHC GT1–GT6. These studies support the pangenotypic use of SOF/VEL for 12 weeks in treatment-naïve and treatment-experienced patients, and those without or with compensated cirrhosis.
    - One pivotal randomised, multicentre Phase III study providing evidence in patients with decompensated cirrhosis and CHC of any genotype (ASTRAL-4). This study supports the pangenotypic use of SOF/VEL+RBV for 12 weeks in those patients with decompensated cirrhosis.
- ASTRAL-1, ASTRAL-2 and ASTRAL-3 were controlled studies:
    - ASTRAL-2 and ASTRAL-3 used an active comparator, SOF+RBV, a licensed and NICE-recommended treatment option for patients with CHC GT2 (12 weeks duration, ASTRAL-2) and GT3 (24 weeks duration, ASTRAL-3).
    - ASTRAL-1 was placebo controlled, which given the pangenotypic characteristics of the patient group enrolled was the most appropriate choice. There is currently no single standard of care that can be used to treat all CHC genotypes over the same treatment duration. Although SOF+Peg-IFN+RBV has demonstrated SVR in all HCV genotypes evaluated, the inclusion of Peg-IFN in a comparator regimen would exclude patients who are ineligible for Peg-IFN due to contraindications or intolerance. In addition, this regimen is not licensed in patients with GT2. The use of a placebo-controlled design allowed for an assessment of the contribution of the active drugs – SOF and VEL – to the safety profile of the active treatment, while the double-blind design reduced the risk of bias in this assessment.
- All ASTRAL-1 studies were multicentre with recognised clinically valid endpoints; ASTRAL-1 and ASTRAL-3 both included a high proportion of patients enrolled at UK sites (ASTRAL-1: n=104 at 11 sites; ASTRAL-3: n=105 at 11 sites).
- The ASTRAL studies provide evidence for a wide range of patient subgroups, including substantial proportions of patients with characteristics that have historically been associated with lower rates of response to IFN-based treatment (27) and that reflect

patient characteristics seen in clinical practice. These include cirrhosis, 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 ASTRAL-1, -2, and -3 showed that SVR12 rates with SOF/VEL regimens were not substantially affected by any predefined characteristic.

- All of the ASTRAL 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.

Limitations:

- ASTRAL-2 and ASTRAL-3 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. In ASTRAL-3 it would also have been necessary for patients in the SOF/VEL arm to take a further 12 weeks of placebo treatment, following the end of SOF/VEL treatment to match the 24-week duration in the SOF+RBV arm, and maintain blinding. This would have meant that the timing of the primary outcome measurement – SVR 12 weeks after the end of treatment – could not have been completed under the same conditions for both treatment arms, and thus introducing bias.
- No UK specific studies have been performed; however, the ASTRAL trials have been conducted in populations that can be considered as broadly representative of the UK population. ASTRAL-1 and ASTRAL-3 recruited patients across North America and Europe, as well as Hong Kong in ASTRAL-1, and Australia and New Zealand in ASTRAL-3. Both studies recruited more than 100 patients across 11 sites in the UK, accounting for 14% and 19% of the trial populations, respectively. ASTRAL-2 and ASTRAL-4 were conducted in the US. However, age and gender demographics of HCV infected patients in the UK and the US are similar (45). Subgroup analyses generally showed that SVR12 rates with SOF/VEL regimens were not affected by any predefined patient characteristic (Section 4.8).

Relevance of the evidence base and outcomes measured

The evidence base presented herein reflects the entirety of the Phase III evidence base supporting the licensed indication for SOF/VEL and 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, cirrhosis and those with prior 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 (14). 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 (160).

Both SVR12 and SVR24 have been accepted as endpoints of therapy by regulators in Europe and the US, due to the high concordance seen between these outcomes (14); in the ASTRAL trials 100% concordance was observed between SVR12 and SVR24 (See Section 4.7).

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 (8, 41, 50-52). In addition, patients experience improved HRQL (44, 53), require reduced healthcare utilisation (54), and importantly, are no longer at risk of transmitting HCV to others.

Through improving cure rates and potentially reducing onward transmission, SOF/VEL 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 hepatitis C are male (3, 45), with a [redacted] This is generally consistent with the age and sex distribution seen across ASTRAL-1, -2 and -3, in which males accounted for 59-62% of patients and the mean age was between 50 and 57 years. In ASTRAL-4 males accounted for 70% of patients, with a slightly higher mean age of 58 years, which may reflect the more advanced nature of liver disease seen in this patient cohort (decompensated cirrhosis). This is closely aligned with the mean age of patients treated in the Expanded Access Programme in England of 54 years (161).

Although ASTRAL-2 and ASTRAL-4 were conducted at US centres exclusively, gender and age demographics of CHC patients in the UK and the US are broadly similar (45).

The majority of patients across all ASTRAL studies were White (79–90%), Asian (2–10%) or Black (1–9%). 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, although some analyses were limited by small numbers (Section 4.8). For example, the proportion of Black patients was very low in ASTRAL-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). All trials include treatment arms that are relevant to the licensed regimens (SOF/VEL or SOF/VEL+RBV) for the recommended treatment duration of 12 weeks.

4.14 *Ongoing studies*

Table 58: SOF/VEL ongoing studies

Study number	Details	Estimated date final results will be available
NCT02625909 (VHCRP1401) “REACT”	Phase 3 SOF/VEL 6 weeks vs SOF/VEL 12 weeks Independent Sponsor: Kirby Institute, Sydney, Australia Sites in North America, Oceania and EU RCT in acute infection with HCV in: • people who inject drugs or	August 2019 Estimated primary completion August 2018

Study number	Details	Estimated date final results will be available
	• HIV co-infected Estimated enrolment 250	
NCT02722837 (GS-US-342-1522)	Phase 3 SOF/VEL 12 weeks Gilead sponsored (Russia & Sweden) registration trial Target enrolment 120 participants	March 2017
NCT02728206 (GS-US-342-2083)	Phase 2 SOF/VEL for 4 weeks post liver transplant In patients receiving a transplanted liver not infected with HCV Target enrolment 10 participants	May 2017
NCT02671500 (GS-US-342-1518)	SOF/VEL 12 weeks Gilead sponsored registration trial in Malaysia & Singapore China, Singapore, Thailand, Malaysia Vietnam Health authorites Target enrolment 360	December 2017

EU, European Union; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RCT, randomised controlled trial; SOF, sofosbuvir, VEL, velpatasvir.

5 Cost effectiveness

5.1 *Published cost-effectiveness studies*

5.1.1 *Identification of studies*

A systematic review was conducted to identify all published studies that had assessed the cost-effectiveness of DAAs for treating CHC. The systematic searches were conducted using the following electronic databases:

- MEDLINE and MEDLINE In-Process (via Ovid SP)
- Embase (via Ovid SP)
- The Cochrane Library (via the Wiley platform), including:
- HTA database
- NHS Economic Evaluations Database (NHS-EED)
- EconLit (via EBSCO)

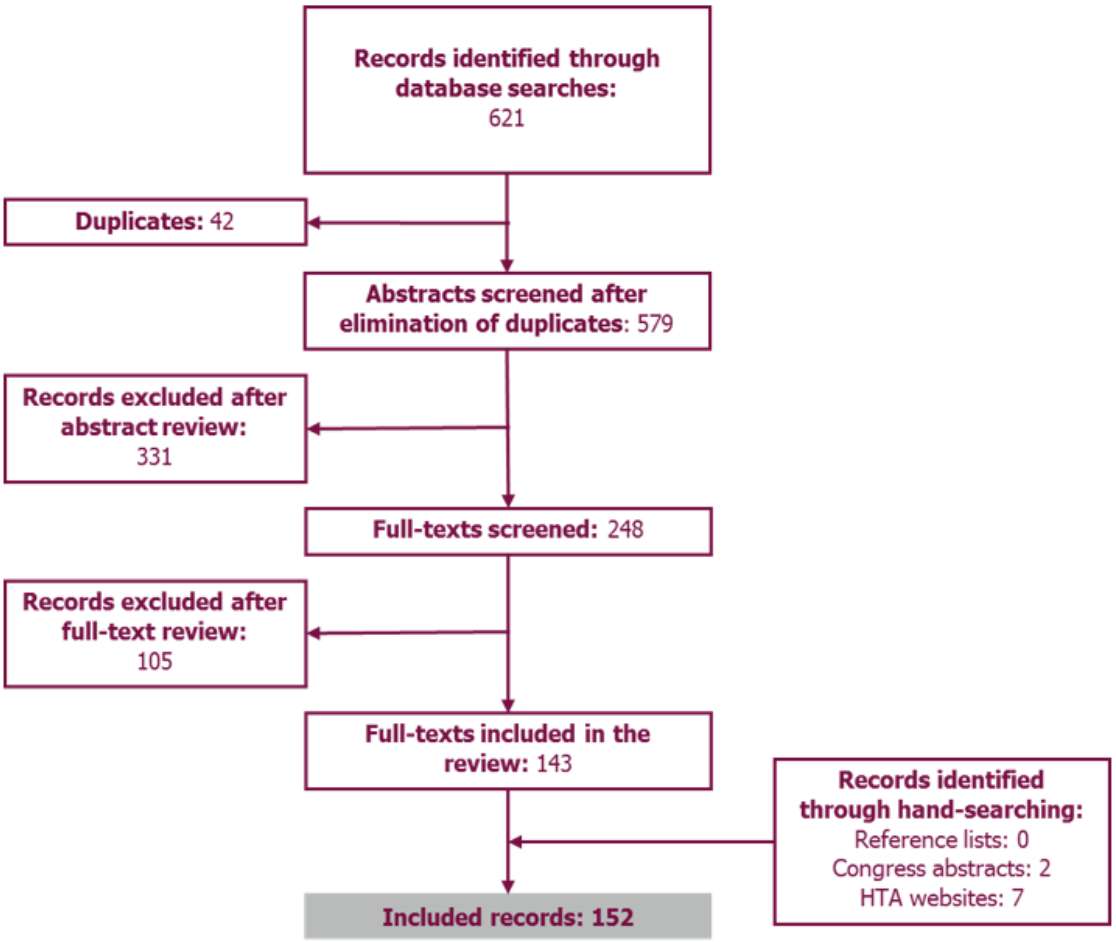
All databases were searched on 24th March 2016.

Full details of the search methodology are provided in Appendix 12.

A total of 621 records were identified through the database searches. After an initial round of de-duplication, 579 records were selected for abstract review. After reviewing all records on the basis of title and abstract, 248 records were selected to be reviewed in full. Following review of these 248 full-texts, 143 were found to fulfil the inclusion criteria.

No further relevant studies were identified through the hand-searching of reference lists. Two relevant economic evaluations were found through the hand searches of congresses. Seven relevant HTA submissions were found. A total of 152 studies were therefore included in this systematic review.

Figure 15: Schematic for the systematic review of cost-effectiveness studies



5.1.2 *Description of identified studies*

There were 25 publications reporting economic evaluations in the UK setting. Given the rapidly changing treatment landscape in CHC and the recent introduction of a number of DAAs into clinical practice in the UK NHS following appraisal by NICE, it was considered most useful to focus the data extraction on economic evaluations conducted in the UK which had specifically evaluated the cost-effectiveness of DAA regimens of particular interest (SOF-, DCV- and OBV-based regimens). These studies were therefore selected for extraction. Conference abstracts or posters were only extracted where they considered a regimen or population not already evaluated in a peer-reviewed publication or HTA submission. Six UK studies were identified as of particular interest and data were extracted.

A summary of the included and excluded UK economic evaluations is provided in Appendix 12, as well as an extraction table for the six UK studies with full details on model methodology, patient population, interventions model and results.

5.1.2.1 Model structure

All six studies were cost-effectiveness analyses, with a clearly defined rationale. They were all cohort Markov state-transition models, which reflects the established modelling methodology of CHC treatments, and the use of transition probabilities (TPs) to reflect the progressive nature of the condition.

For any economic evaluation, the time horizon considered in the analysis should be long enough to capture the entire difference in costs and outcomes of the alternative strategies. All six studies had a lifetime time horizon, to reflect the disease modifying nature of DAA therapies and their lifelong impact.

5.1.2.2 Model parameters

Health state utility values representing the HCV-related quality of life at different disease states were reported by most of the studies reviewed, however not all were identified via a systematic literature review.

The speed at which patients move between the Markov states are defined as TPs. Disease state transitions adopted across the six extracted studies were between METAVIR fibrosis stages, mild to moderate disease, and transitions to advanced liver disease.

Sources for resource use and cost data were routinely provided, however these were not always identified via a systematic literature review. Trial reported SVR rates were used to quantify the impact of a treatment on a person's condition. Across the six studies, extensive sensitivity analysis was conducted.

5.1.3 *Quality assessment of identified studies*

Quality assessments are provided in Appendix 13.

5.2 *De novo analysis*

5.2.1 *Patient population*

An economic evaluation was conducted to determine the cost-effectiveness of SOF/VEL treatment in people with CHC. These patient groups are defined by HCV genotype including those with decompensated cirrhosis, and any previous treatment for CHC (treatment-naïve or -experienced). In addition, NICE has previously recommended some treatments only for patient groups who are ineligible for IFN. Therefore, separate economic analyses have been conducted to determine the cost-effectiveness of SOF/VEL for these populations. Furthermore, for patients with GT2 and GT3 who are treatment-naïve and non-cirrhotic, the only treatment that is currently recommended by NICE without restriction is Peg-IFN+RBV; for patients within these groups who are ineligible for IFN or RBV, separate analyses of the cost-effectiveness of SOF/VEL have also been conducted (the relevant comparator for these groups is no treatment given that no alternative options have been recommended by NICE).

The specific populations are:

- GT1 (including GT1a, GT1b and combined GT1a and 1b)

- GT2
- GT3
- GT4
- GT5
- GT6
- Decompensated cirrhosis

These populations reflect both the licensed indications for SOF/VEL therapy, as well as the patient populations recruited to the Phase II/II SOF/VEL studies. Table 59 reports the subgroups investigated in the model.

Table 59: Model populations and genotypes

GT	Previous CHC treatment		Non-cirrhotic	Cirrhotic	DCC	IFNi
	Naive	Experienced				
GT1a	X	X	X	X		X
GT1b	X	X	X	X		X
GT1	X	X	X	X		X
GT2	X	X	X	X		X
GT3	X	X	X	X		X
GT4	X	X	X	X		X
GT5	X	X	X	X		
GT6	X	X	X	X		
All genotypes	X	X			X	

CHC, chronic hepatitis C; DCC, Decompensated cirrhosis; GT, genotype; IFNi, interferon-ineligible.

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.

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 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.

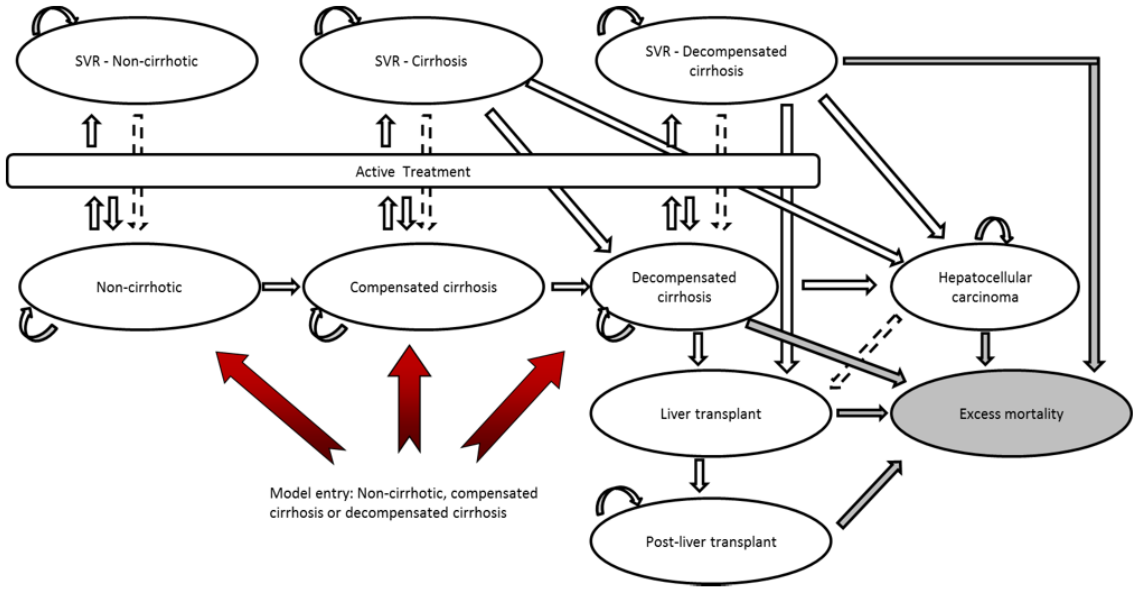
5.2.2 *Model structure*

5.2.2.1 Type of de novo analysis

A Markov state-transition model was adapted from the model by Dusheiko and Roberts, (1995) (29). 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 16. The same model structure is used for all patients irrespective of HCV genotype or treatment experience. The model consists of ten health states with TPs between the states, and costs, mortality and morbidity associated with each state.

Figure 16: Model schematic



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.

5.2.2.2 Justification of the chosen structure

A Markov state-transition model was adapted from the model by Dusheiko and Roberts, 1995 (29) 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 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 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, in which patients were split between non-cirrhotic and cirrhotic defined as per the Fibrotest and Fibroscan scores. A liver biopsy was not required to confirm the presence or absence of cirrhosis, which is used to determine the level of fibrosis in the non-cirrhotic state. This also reflects that an invasive liver biopsy is no longer standard clinical practice in the UK CHC treatment pathway.

5.2.2.3 Clinical pathway and health states

The definitions of the individual health states are provided in Table 60.

Table 60: Health state definitions

State	Definition
Non-cirrhotic	Fibroscan (in countries where locally approved) with a result of ≤12.5 kPa within ≤6 months of Baseline/Day 1† Fibrotest score of ≤0.48 and an APRI of ≤1 performed during screening†
Compensated cirrhosis	Fibroscan (in countries where locally approved) showing cirrhosis or results ≥12.5 kPa† Fibrotest score of >0.75 and an AST: platelet ratio index (APRI) of >2 performed during screening†
Decompensated cirrhosis	Clinical (major symptomatic)‡ & histological (cirrhosis)
SVR – Non-cirrhotic	Virologic, 12/24 weeks after the end of therapy
SVR – Compensated cirrhosis	Virologic, 12/24 weeks after the end of therapy
SVR – Decompensated cirrhosis	Virologic, 12/24 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; kPa, Kilopascal; SVR, Sustained virologic response.
† Source: Gilead clinical trials protocols; ‡ Major symptomatic = Encephalopathy, Coagulopathy, Variceal bleed.

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

- Liver biopsy showing cirrhosis (METAVIR score=4 or Ishak score ≥ 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 follows:

- 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 61.

Table 61: 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

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 16, the on-treatment phase ("Antiviral treatment") directs patients in the model to either:

- SVR health states of either "SVR – Non-cirrhotic", "SVR – Cirrhosis" or "SVR – Decompensated 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 16. These assumptions of disease progression have also been used by Grishchenko et al, 2009 (164) Hartwell et al, 2011 (163) and Shepherd et al, 2007 (162).

Non-cirrhotic and cirrhotic patients move to the SVR health state after completing treatment if they have undetectable HCV RNA 12 or 24 weeks after end of treatment, otherwise referred to as a cure. A patients 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 (DCC) 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.

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 (165).

Patients in both compensated and decompensated cirrhosis can progress to HCC stage, with its associated costs and 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 compensated 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 by the grey coloured arrows in Figure 16.

5.2.2.4 Key features of the de novo analysis

Table 62: Key features of the de novo analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (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 previously reflected in NICE HTAs, due to the nature of CHC, lifetime horizon allows capturing the difference between SOF/VEL and the comparators in terms of long-term costs and health benefits. 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.	(162, 163)
Were health effects measured in QALYs; if not, what was used?	QALYs	As per NICE reference case	(166)
Discount of 3.5% for utilities and costs	3.5% for utilities and costs	As per NICE reference case	(166)
Perspective (NHS/PSS)	NHS and PSS	As per NICE reference case	(166)
Cycle length	The model employs two-week cycle lengths for the first 72 weeks, followed by 24-week cycle length for 24 weeks. Thereafter, transitions occur on an	Treatment durations of comparators vary from 8 weeks to 48 weeks. Shorter initial cycles allowed modelling different treatment strategies with patients transiting to health state with SVR (either SVR12 or SVR24) in the	(162-165, 167)

Factor	Chosen values	Justification	Reference
	annual basis	same model at different cycles.	
Half-cycle correction	Applied from year 3 onwards (yearly transitions)	Patients transition throughout the cycle and not only at the beginning/end of each cycle. This is also consistent with previous HTAs. Half-cycle correction applied from year 3 onwards since shorter cycle lengths were applied in years 1-2.	Hartwell et al, 2011 (163) Shepherd et al, 2007 (162)

CHC, chronic hepatitis C; HTA, Health Technology Assessment; NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years; SOF, Sofosbuvir; SVR, Sustained virologic response; VEL, Velpatasvir.

5.2.3 *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 63 to Table 77. The first set of tables cover each set of comparators by genotype (Section 5.2.3.1). The next set cover IFN-ineligible populations (Section 5.2.3.2). The final table covers decompensated cirrhosis (Section 5.2.3.3). Some comparators of relevance to the decision problem were not included in the original economic model, and because of the way in which the economic model was constructed it was not possible to introduce these into the base-case analyses. Where possible these comparators have been considered in scenario analyses and are marked as such in the preceding tables.

SOF/VEL (400/100mg once daily) is awaiting market authorisation from the EMA. This formulation for 12 weeks (SOF/VEL (12 wks) is the active treatment across all GTs and populations, except in the DCC population, where SOF/VEL+RBV (12 wks) is the active treatment. No stopping rules, lead in phases or additional treatments are considered for SOF/VEL based regimens. Treatment combinations and length of treatment stratified by GT are listed in the treatment duration sections of each indication (Section 5.6.1).

5.2.3.1 Genotypes

Table 63: Comparator treatments: GT3

Indication		Comparator
TN	NC	No treatment
		Peg-IFN2a + RBV (24 wks)
	CC	No treatment
		Peg-IFN2a + RBV (24 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
TE	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)

CC, cirrhotic; NC, non-cirrhotic; Peg-IFN, Pegylated interferon; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

Table 64: Comparator treatments: GT1a

Indication		Comparator
TN	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (8 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)
		Sofosbuvir + daclatasvir (12 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)
TE	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)
		Sofosbuvir + daclatasvir (12 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)

CC, cirrhotic; NC, non-cirrhotic; Peg-IFN, Pegylated interferon; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

Table 65: Comparator treatments: GT1b

Indication		Comparator
TN	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (8 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)
		Sofosbuvir + daclatasvir (12 wks)

Indication		Comparator
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)
TE	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)
		Sofosbuvir + daclatasvir (12 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)

CC, cirrhotic; NC, non-cirrhotic; Peg-IFN, Pegylated interferon; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

Table 66: Comparator treatments: GT1

Indication		Comparator
TN	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (8 wks)
		Sofosbuvir + daclatasvir (12 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)
TE	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)

Indication		Comparator
		Sofosbuvir + daclatasvir (12 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Simeprevir + Peg-IFN2a + RBV (RGT)

CC, cirrhotic; NC, non-cirrhotic; Peg-IFN, Pegylated interferon; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

Table 67: Comparator treatments: GT2

Indication		Comparator
TN	NC	No treatment
		Peg-IFN2a + RBV (24 wks)
	CC	No treatment
		Peg-IFN2a + RBV (24 wks)
TE	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Sofosbuvir + RBV (12 wks)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Sofosbuvir + RBV (12 wks)

CC, cirrhotic; NC, non-cirrhotic; Peg-IFN, Pegylated interferon; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

Table 68: Comparator treatments: GT4

Indication		Comparator
TN	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)
		Simeprevir + Peg-IFN + RBV RGT†
		Daclatasvir + Peg-IFN + RBV (daclatasvir 24w + Peg-IFN/RBV for 48w)†
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
		Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)†
		Simeprevir + Peg-IFN + RBV RGT†
		Daclatasvir + Peg-IFN + RBV (daclatasvir 24w + Peg-IFN/RBV for 48w)†

Indication		Comparator
TE	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)
		Sofosbuvir + daclatasvir (12 wks)†
		Simeprevir + Peg-IFN + RBV RGT†
		Daclatasvir + Peg-IFN + RBV (daclatasvir 24w + Peg-IFN/RBV for 48w)†
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Sofosbuvir + Peg-IFN + RBV (12 wks)
		Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)†
		Simeprevir + Peg-IFN + RBV RGT†
		Daclatasvir + Peg-IFN + RBV (daclatasvir 24w + Peg-IFN/RBV for 48w)†

CC, cirrhotic; NC, non-cirrhotic; Peg-IFN, Pegylated interferon; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.
† Scenario analyses only.

Table 69: Comparator treatments: GT5

Indication		Comparator
TN	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)
TE	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)

CC, cirrhotic; NC, non-cirrhotic; Peg-IFN, Pegylated interferon; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

Table 70: Comparator treatments: GT6

Indication		Comparator
TN	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)

Indication		Comparator
TE	NC	No treatment
		Peg-IFN2a + RBV (48 wks)
	CC	No treatment
		Peg-IFN2a + RBV (48 wks)
		Sofosbuvir + Peg-IFN2a + RBV (12 wks)

CC, cirrhotic; NC, non-cirrhotic; Peg-IFN, Pegylated interferon; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

5.2.3.2 IFN-ineligible

Table 71: Comparator treatments: GT3 IFN-ineligible

Indication		Comparator
TN	NC	No treatment
		Sofosbuvir + daclatasvir (12 wks)
	CC	No treatment
		Sofosbuvir + daclatasvir + RBV (24 wks)
		Sofosbuvir + RBV (24 wks)
TE	NC	No treatment
		Sofosbuvir + daclatasvir (12 wks)
	CC	No treatment
		Sofosbuvir + daclatasvir + RBV (24 wks)
		Sofosbuvir + RBV (24 wks)

CC, cirrhotic; NC, non-cirrhotic; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

Table 72: Comparator treatments: GT2 IFN-ineligible

Indication		Comparator
TN	NC	No treatment
		Sofosbuvir + RBV (12 wks)
	CC	No treatment
		Sofosbuvir + RBV (12 wks)
TE	NC	No treatment
		Sofosbuvir + RBV (12 wks)
	CC	No treatment
		Sofosbuvir + RBV (12 wks)

CC, cirrhotic; NC, non-cirrhotic; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

GT1a/1b/1/4 IFN-ineligible populations were all modelled as scenario analyses.

- In the case of GT1a/1b/1 cirrhotic patients the only difference in NICE recommendations for IFN-free regimens between overall populations and those who are IFN-ineligible is for SOF+DCV+RBV 24 weeks which is restricted to IFN-

ineligible. This comparator could not be included in the base-case analysis and thus the IFN-ineligible comparison was considered as a scenario

- In the case GT1a/1b/1 non-cirrhotic NICE recommendations do not restrict any IFN-free containing regimen by IFN-ineligibility, and hence GT1a/1b/1 non-cirrhotic IFN-ineligible was not modelled
- In the case of GT4 cirrhotic patients the only difference in NICE recommendations for IFN-free regimens between the overall populations and those who are IFN-ineligible is that SOF+DCV+RBV 24 weeks is restricted to GT4 cirrhotic IFN-ineligible patients. This comparator could not be included in the base-case analysis and thus the IFN-ineligible comparison was considered as a scenario
- In GT4 treatment-naïve non-cirrhotic patients the only difference in NICE recommendations for IFN-free regimens is for SOF+DCV 12 weeks which is restricted to IFN-ineligible patients. This comparator could not be included in the base-case analysis and thus the IFN-ineligible comparison was considered as a scenario
- GT4 treatment-experienced non-cirrhotic IFN-ineligible is modelled as a scenario as per the overall GT4 population to incorporate SOF+DCV 12 weeks

Table 73: Comparator treatments: GT1a IFN-ineligible

Indication		Comparator
TN	CC	No treatment
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)
		Sofosbuvir + daclatasvir + RBV (24 wks)
TE	CC	No treatment
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)
		Sofosbuvir + daclatasvir + RBV (24 wks)

CC, cirrhotic; NC, non-cirrhotic; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

Table 74: Comparator treatments: GT1b IFN-ineligible

Indication		Comparator
TN	CC	No treatment
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)
		Sofosbuvir + daclatasvir + RBV (24 wks)
TE	CC	No treatment
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)
		Sofosbuvir + daclatasvir + RBV (24 wks)

CC, cirrhotic; NC, non-cirrhotic; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

Table 75: Comparator treatments: GT1 IFN-ineligible

Indication		Comparator
TN	CC	No treatment
		Ledipasvir/sofosbuvir (12 wks)
		Sofosbuvir + daclatasvir + RBV (24 wks)
TE	CC	No treatment
		Ledipasvir/sofosbuvir (12 wks)
		Sofosbuvir + daclatasvir + RBV (24 wks)

CC, cirrhotic; NC, non-cirrhotic; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

Table 76: Comparator treatments: GT4 IFN-ineligible

Indication		Comparator
TN	NC	No treatment
		Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)
		Sofosbuvir + daclatasvir (12 wks)
	CC	No treatment
		Ledipasvir/sofosbuvir (12 wks)
		Sofosbuvir + daclatasvir + RBV (24 wks)
		Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)
TE	NC	No treatment
		Sofosbuvir + daclatasvir (12 wks)
		Ledipasvir/sofosbuvir (12 wks)
		Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)
	CC	No treatment
		Ledipasvir/sofosbuvir (12 wks)
		Sofosbuvir + daclatasvir + RBV (24 wks)
		Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)

CC, cirrhotic; NC, non-cirrhotic; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

5.2.3.3 Decompensated cirrhosis

Table 77: Comparator treatments: Decompensated cirrhosis all genotypes

Indication	Comparator
TN	Ledipasvir/sofosbuvir + RBV 12 weeks
TE	Ledipasvir/sofosbuvir + RBV 12 weeks

DCC, decompensated cirrhosis; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

5.3 *Clinical parameters and variables*

5.3.1 *How are clinical data incorporated into the model?*

Key clinical data are listed in Table 78 and described further in the following sub sections.

Table 78: Clinical data implemented in the economic model

Characteristics	Data	Sources
Patient characteristics	Mean age at treatment initiation Weight Probability of death	Published literature for mean age and weight (163) and probability of death (168) Assumptions applied for some genotypes (see Table 79)
Treatment characteristics	SVR rates Rates of AEs Treatment durations	SOF/VEL clinical trials Comparator treatment trials and literature Expert opinion
Health related quality of life	Relative on treatment decrements	SOF/VEL clinical trials Comparator treatment trials and literature

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

5.3.1.1 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 and are presented for each indication in Table 79.

Table 79: Patient characteristics

Indication	Mean age at treatment (yrs)	Mean weight (kg)
GT1aTN	40	79
GT1aTE	45	79
GT1bTN	40	79
GT1bTE	45	79
GT1TN (GT1a 65%, GT1b 35%)	40	79
GT1TE (GT1a 65%, GT1b 35%)	45	79
GT2TN	40	79
GT2TE	45	79
GT3TN	40	79
GT3TE	45	79
GT4TN	40	79
GT4TE	45	79
GT5TN	40	79
GT5TE	45	79
GT6TN	40	79
GT6TE	45	79
DCCTN	55	79
DCCTE	60	79

DCC, Decompensated cirrhosis; GT, Genotype; TE, Treatment-experienced; TN, Treatment-naïve; yrs, years
Source: Hartwell et al, 2011 (163) for GT1 and GT3, Assumption for GT2, 4, 5, 6 and DCC

5.3.1.2 Background mortality – probability of death

Background mortality was applied in the model using the Office for National Statistics (2012–2014) National Life Tables for England. It was assumed that the population entering the model comprises 61% men and 39% females (165). The table of age-related mortality probabilities is provided in Appendix 14.

5.3.1.3 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 and comparators were obtained from relevant trials or SmPCs; study design and patient characteristics for these sources are described in Section 4.10.9 for each population of relevance. SVR rates used in the modelling are described in Section 5.6.1. As described in Section 4.10, naïve comparisons were the most appropriate source of clinical efficacy data for the economic analysis, due to limitations in the NMA. To re-iterate, the results of the NMA were not considered robust or credible for use in the economic model. In the GT3 treatment-naïve network, given the requirement to include results from the ELECTRON trial, and the heterogeneity introduced in the network from pooling data from cirrhotic and non-cirrhotic patients, using the results of the NMA directly in the economic model would not be robust and therefore naïve comparisons using SVR rates from the most appropriate individual trials was more appropriate. This is particularly justifiable in the context of the NICE scope, which requires economic model analyses to be stratified by treatment history and cirrhosis status, for each genotype. Data inputs for SOF/VEL and the comparator regimens are varied in deterministic sensitivity analysis to address the uncertainty in this approach.

Rates of Grade 3 and 4 AEs for SOF/VEL and comparators were obtained from relevant trials or SmPCs and are described in Section 5.6.1. Unit costs of treating AEs were applied, as described in Section 5.5.4.

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

5.3.1.4 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. The utility increment for SOF/VEL (12wks) was assumed equal to the ION trials for LDV/SOF (12wks).

5.3.2 *Transition probabilities*

The TPs used in the model are reported in Table 81. In general, the TPs chosen were those used by the latest UK HTAs (such as Hartwell et al, 2011 and Shepherd et al, 2007 and those used by Grishchenko et al, 2009, which were taken from a large representative sample of UK centres (162-164)).

In the LDV/SOF submission to NICE (TA330), the ERG commented that the details provided about how TPs for the non-cirrhotic state to the compensated cirrhosis health state had been estimated, were insufficient to critique the robustness of the approach taken.

This transition is of particular importance given the evidence that suggests that genotype affects the rate of disease progression, with GT3 being linked to faster progression versus other genotypes. GT3 virus has been observed to have a direct impact on intermediary hepatic lipid metabolism (169-171) in a manner not observed with GT1 virus. The result of this is an intrahepatic accumulation of lipid (steatosis), which underlies the accelerated fibrosis progression observed in GT3 infection (43). When untreated or unresponsive to treatment, persistent GT3 infection is also associated with a doubling of risk of HCC compared with non-GT3 infection (7). In order to ascertain the most appropriate data source for the model TP from non-cirrhotic to compensated cirrhosis, a targeted literature review of studies which reported fibrosis progression rates in GT3 was conducted, with a particular focus on studies of GT3 patients. Details of the search strategy and the flow diagram of identified studies are provided in Appendix 15. While 16 studies met the inclusion criteria, 11 studies specifically reported data for the model transition of particular interest (non-cirrhotic to compensated cirrhosis states) and therefore, these studies are discussed in more detail below.

The 11 relevant studies ranged in size, geography and publication year, with the majority sampling from populations ≤105 people. For 10 of the 11 identified studies, one of two methods were used for calculating the annual TP from non-cirrhotic to compensated cirrhosis states. Descriptions of these methods are provided in Appendix 15.

For one of the identified studies (Kanwal, 2009 (172)) 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 as shown in Table 80).

This resulting transition probabilities calculated for the non-cirrhotic to compensated cirrhosis transition in the 11 identified studies are listed in Table 80.

Table 80: Transition probabilities derived for non-cirrhotic to compensated cirrhosis

Study	Mean baseline age	Number of patients included In study	Calculated transition probability
Adinolfi, 2001 (169)	40[†‡]	26	0.025
Bochud, 2009 (173)	40[†‡]	312	0.038
Cross, 2009 (174)	44[§]	30	0.012
Fartoux, 2005 (175)	38.5	22	0.036
Hissar, 2009 (176)	41.6	105	0.060
Kanwal, 2014 (172)	50.2[†]	8,337	0.030
Poynard, 1997 (177)	45.6	39	0.038
Reiberger, 2010 (178)	37[§]	24	0.048
Sierra, 2003 (179)	37.7	56	0.035
Westin, 2002 (180)	35.6[‡§]	22	0.032
Zarski, 2003 (181)	26[¶]	21	0.044

† GT3 specific; ‡ Denotes median; § Age at first biopsy; ¶ Mean age at infection

By far the largest, as well as being the most recent study, was by Kanwal et al (2014) (172). 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, and pan-genotypic coverage. When compared with the remaining 10 studies outlined in Table 80, the TP from the Kanwal study (0.030) lies within the reported range of corresponding GT3 TPs (0.025 to 0.06). In fact, as the third lowest TP among the identified studies, the Kanwal study appears to offer a conservative measure of the actual risk of disease progression in GT3.

As discussed in Section 5.3.3 (clinical validation), external clinical expert opinion was sought on the applicability of the Kanwal study data to a UK setting. The clinical experts confirmed that the Kanwal data were aligned with current expert opinion regarding more rapid disease progression in patients with GT3 infection compared with other genotypes. While not a UK-specific study, the cohort in the Kanwal dataset appeared broadly relevant to the demographics of the UK CHC epidemic, and the size of the dataset was compelling.

In addition, GT3-infected patients of South Asian origin form a significant proportion of the GT3 population in the UK, [redacted]

[redacted] These patients would likely be underrepresented in a study of US veterans. The relevance of this is clear when the study by Hissar (2009) (176) is considered. This study was conducted in India and reported outcomes in 105 Indian patients of mean age 41.6 years at baseline. The calculated TP was almost double that observed in the Kanwal study, at 0.060. Clinical expert opinion was that, although there may be confounding factors behind this even faster progression rate beyond ethnicity, it did suggest a clinical consideration of concern for treatment in this subgroup of patients and is likely to contribute to the adoption of the Kanwal dataset as being a conservative measure of GT3 disease progression risk in the UK setting.

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 81.

One study was conducted in a UK setting (Cross 2009 (174)). This was a single centre, retrospective analysis of those who had two or more liver biopsies in the past. The small sample size (n=30) of this study renders the results more open to uncertainty. In addition, the study has inherent potential selection bias in that, of 837 included patients, only 139 had a paired liver biopsy, from which the thirty studied genotype 3 patients were a derived subset. Within the paired biopsy group, it is possible that over the interval between biopsies, they would be more likely to represent patients who had not experienced disease progression, given that 72% of the group had started at fibrosis stage 2 or 3 and the median duration of follow-up was 50 months (IQR 34-74 months). Furthermore, a second biopsy is less likely to be performed to assess progression in those patients in whom the diagnosis of cirrhosis is obvious through other means of assessment, such as radiologic imaging in association with a clinical assessment consistent with disease progression. Within the majority of included patients who had one biopsy, no data on disease progression has been presented with which to compare outcomes. However, it is not unreasonable to expect that there may have been progression-related reasons for these patients not having a second biopsy.

Previous economic evaluations and HTAs also indicated that TPs between advanced health states are not age-dependent (162, 163, 165, 167).

Table 81: Transition probabilities used in the model

From	To	Annual TP	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 (172)	Assumes GT5 and GT6 are equivalent to GT4
Compensated cirrhosis	Decompensated cirrhosis	0.0438	Cardoso et al 2010 (50)	Calculated Cardoso included patients stage at F3 and F4 and DCC was defined as

				several liver-related complications
	HCC	0.0631	Cardoso et al 2010 (50)	Calculated
Compensated cirrhosis SVR	Decompensated cirrhosis	0.0064	Cardoso et al 2010 (50)	Calculated Cardoso included patients stage at F3 and F4 and DCC was defined as several liver-related complications
	HCC	0.0128	Cardoso et al 2010 (50)	Calculated
Decompensated cirrhosis	HCC	0.0631	Cardoso et al 2010 (50)	Calculated
	Liver transplant	0.022	Siebert 2005 (182)	
	Death	0.24	EAP data (EASL 2016) (161)	
Decompensated cirrhosis SVR	HCC	0.0631	Assumption	Assumed same as TP from DCC without SVR
	Liver transplant	0.022	Assumption	Assumed same as TP from DCC without SVR
	Death	0.049	EAP data (EASL 2016) (161)	
HCC	Death	0.4300	Fattovich et al, 1997 (183)	Obtained from Shepherd et al, 2007 (162)
Liver transplant	Death, Yr1	0.2100	Bennett et al 1997 (184)	Obtained from Shepherd et al, 2007 (162)

DCC, decompensated cirrhosis; EAP, Expanded Access Programme; GT, Genotype; HCC, Hepatocellular carcinoma; HIV, Human immunodeficiency virus; SVR, Sustained virologic response; TP, Transition probability; Yr, Year

5.3.3 *Clinical expert assessment of applicability of clinical parameters*

This model was based on the model submitted to NICE for the appraisal of sofosbuvir. The model structure, assumptions, and inputs for the previous sofosbuvir model were 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 adverse events 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 eight clinical experts from England and Scotland.

Since these assumptions have been consistently used in both the SOF/VEL, LDV/SOF and the sofosbuvir 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 sofosbuvir 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 review described in Section 5.3.2, the clinical experts agreed that the size of the CHC patient population analysed in the Kanwal study (172), and its recent date of publication, supported its use as a source of genotype-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 clinical experts reviewed the GT1 treatment-naïve and GT3 treatment-naïve network diagrams and forest plots presented in Section 4.10. It was agreed that the approach taken to constructing the treatment networks appeared to be sound from a methodological perspective, but that the results suggested by the forest plots appeared to lack credibility from a clinical perspective. For example, while a difference in SVR of 15% between SOF/VEL and Peg-IFN+RBV in GT3 treatment-naïve patients shown by the NMA would be important from a clinical perspective, data from relevant Phase III trials including ASTRAL-3 and FISSION would tend to suggest that this treatment effect is likely to be greater in practice. The clinical experts discussed potential explanations of why the treatment network in GT3 TN patients would give rise to treatment effects that were smaller than anticipated. It was acknowledged that using the Phase II ELECTRON trial data were necessary in order to construct a network of treatments in GT3 treatment-naïve patients. However, it is known that the data from the ELECTRON trial (showing an efficacy for SOF+RBV 12 weeks in GT3 treatment-naïve patients of 100% SVR) are widely acknowledged to be unrepresentative of usual clinical practice. Inclusion of these data would therefore appear potentially to introduce bias in the overall treatment network. The clinical experts also considered the inability of the network meta-analysis to stratify relative treatment effects according to baseline Metavir score. It was acknowledged that the included trials contained a variable proportion of patients who had cirrhotic disease, and that the efficacy of some treatments (in particular, but not exclusively, Peg-IFN+RBV) would be expected to differ according to the presence or absence of cirrhosis. It was acknowledged that the heterogeneity introduced by an inability to stratify by Metavir score would also be likely to introduce bias in the overall network. As such, the clinical experts agreed that using the relative treatment effects from the network meta-analysis in the economic model comparisons was unlikely to be robust and that alternative approaches to modelling would be recommended.

5.4 *Measurement and valuation of health effects*

5.4.1 *Health-related quality-of-life data from clinical trials*

Please find the details for treatment-specific HRQL utility increments and decrements derived from clinical studies in the base-case de novo model inputs Section 5.6.1.

5.4.2 *Mapping*

The ION trials for LDV/SOF report SF-36 data. These were converted to the SF-6D generic HRQL instrument using the non-parametric Bayesian algorithm provided by the University of Sheffield. This process was also applied for FISSON, FUSION and NEUTRINO trials for SOF (+Peg-IFN+RBV or +RBV). The ION trial SF-6D on-treatment utility values for LDV/SOF were applied to SOF/VEL, due to a lack of available evidence from the ASTRAL trials at the time of submission.

SF-6D values were used directly, rather than mapped to the EQ-5D, due to no clear consensus regarding the most appropriate mapping algorithm.

5.4.3 *Health-related quality-of-life studies*

5.4.3.1 Identification of studies

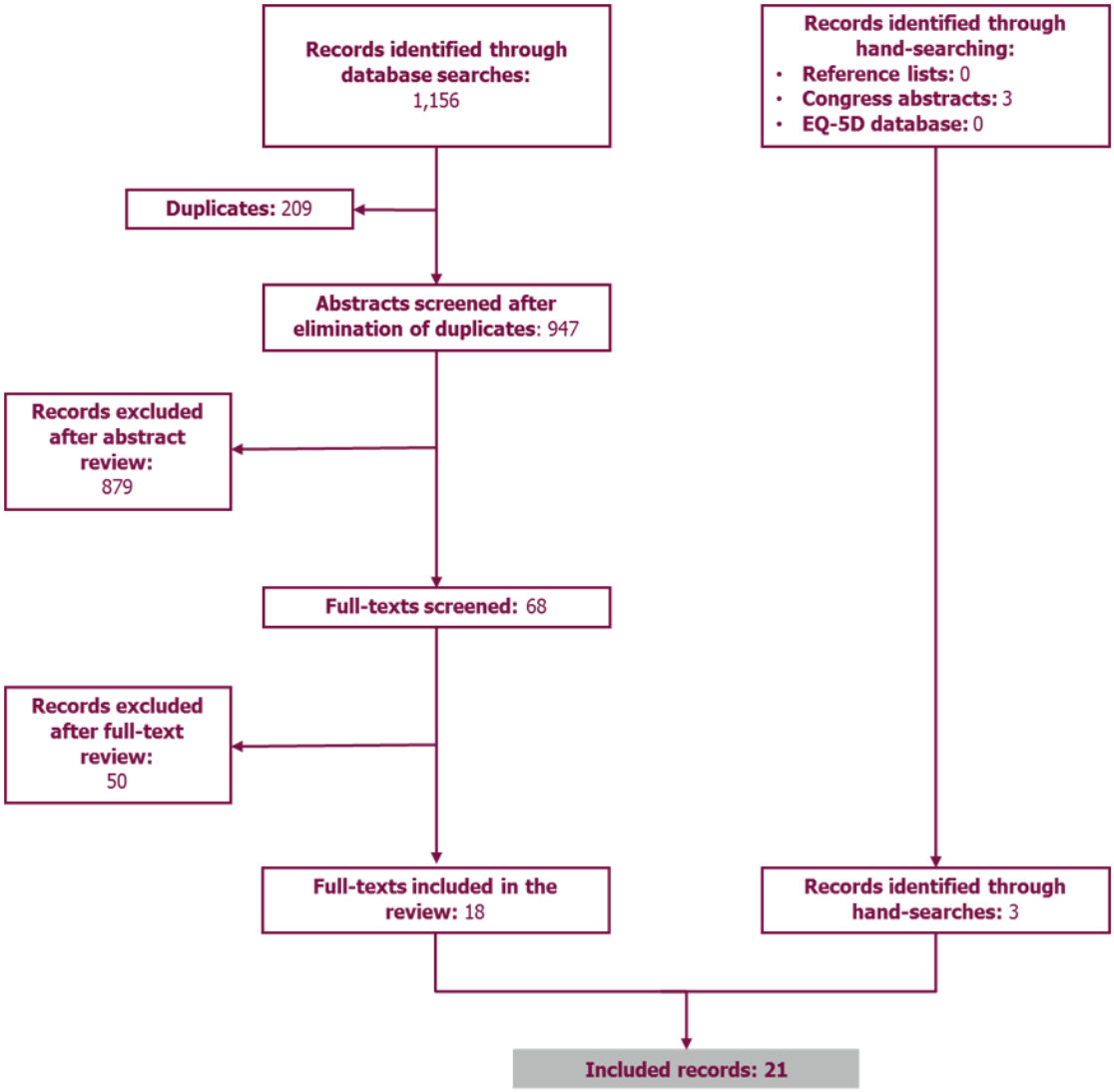
A systematic review was conducted to identify HRQL studies from the published literature relevant to the decision problem.

The following electronic databases were searched: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (Ovid), The Cochrane Library and Econlit (Ovid).

Electronic searches were supplemented by hand searching the bibliographies of systematic reviews, meta-analyses, HTAs and economic evaluations identified through the electronic database searches. The EQ-5D website and specified conference proceedings from 2014–2016 were also searched. Full details of the search are provided in Appendix 16.

In total, 1,156 papers were identified through the electronic searches. Upon the removal of duplicate papers, 947 titles and abstracts were reviewed. Sixty-eight were screened at full paper review stage, of which 50 were excluded. Three records were identified through hand-searches, resulting in 21 relevant papers for final inclusion (Figure 17). These 21 studies examined different aspects of HRQL in CHC patients were included in the review. A summary of the characteristics of included publications in provided in Appendix 16.

Figure 17: Schematic for the systematic review of HRQL evidence



5.4.4 *Key differences between trial derived and literature derived values*

Not applicable. The utility decrements used in the economic model while on treatment (both active treatment and comparators) were obtained from clinical studies. Hence, there are no values in the economic literature to compare with.

5.4.5 *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. The overall impact for all treatments in the economic model were captured from clinical trial data.

5.4.6 *Health-related quality-of-life data used in cost-effectiveness analysis*

Baseline quality of life 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 82. 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 5.1 and 5.4.3. The utilities chosen for the current model were those also used by UK HTAs (Hartwell et al, 2011 (163), Shepherd et al, 2007 (162)) and were predominantly based on the UK trial on mild HCV by Wright et al, 2006 (165). 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 (165), however the value used in this model is based on data from Vera-Llonch et al, 2013 (165), selected as the most recent data with the least uncertainty.

As illustrated by Wright et al, 2006 (165), HRQoL declines as CHC disease progresses to more advanced disease health states (Table 82). 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) (165).

Table 82: Quality of life values

Health-state	Utility	Source	Comments
Baseline – non-cirrhotic	0.75	Wright et al, 2006 (165) (UK mild HCV trial)	Average of mild and moderate utilities assuming 83% mild and 17% moderate EQ-5D Publications that used this utility: -Hartwell et al, 2011 (163) -Grishchenko et al, 2009 (164) -Shepherd et al, 2007 (162)
Baseline – compensated cirrhosis	0.55	Wright et al, 2006 (165) (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al, 2011 (163) -Grishchenko et al, 2009 (164)
Baseline - decompensated cirrhosis	0.45	Wright et al, 2006 (165) (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al, 2011 (163) -Grishchenko et al, 2009 (164) -Shepherd et al, 2007 (162)
SVR (utility increment)	0.04	Vera-Llonch et al, (2013) (185)	Most recent data with less uncertainty than Wright et al, (2006) (165)

Health-state	Utility	Source	Comments
Non-cirrhotic with SVR	0.79	Calculation	
Compensated cirrhotic with SVR	0.59	Calculation	
Decompensated cirrhotic with SVR	0.49	Calculation	
Hepatocellular carcinoma	0.45	Wright et al, (2006) (165) (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al, 2011 (163) -Grishchenko et al, 2009 (164) -Shepherd et al, 2007 (162)
Liver transplant	0.45	Wright et al, 2006 (165) (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al, 2011 (163) -Shepherd et al, 2007 (162)
Post-liver transplant	0.67	Wright et al, 2006 (165) (UK mild HCV trial)	EQ-5D Publications that used this utility: --Hartwell et al, 2011 (163)

EQ-5D, EuroQol-5 dimension; HCV, Hepatitis C virus; SVR, Sustained virologic response.

Liver fibrosis does not occur at the same rate in all individuals, and does not seem to progress linearly. During 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 quality of life 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. The model assumes a decline in QoL when patients progress from non-cirrhotic health states to compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplant. However, an increase in QoL is modelled when patients achieve SVR or after liver transplant (see Table 82). The utility is assumed the same for all patients in any given health state regardless of how long they have been in that state.

5.4.6.1 Clinical expert assessment of applicability of health state utility values

Health state utility values used in the SOF/VEL model do not differ from those employed in the previous LDV/SOF submission to NICE. Therefore, no further clinical expert input was sought on these inputs for the SOF/VEL submission.

5.5 *Cost and healthcare resource use identification, measurement and valuation*

A systematic review of the literature was performed to identify any additional resource data published since the SOF and LDV/SOF NICE submissions, and is reported in Appendix 17: Cost and healthcare resource identification, measurement and valuation. No additional relevant sources were identified, and hence sources and values used were consistent with those used in the previous SOF and LDV/SOF submissions, and previously accepted by NICE. Values were, however inflated to the 2014/2015 cost year. In addition, the SR updates of cost-effectiveness evaluations and HRQL described previously in Sections 5.1 and 5.4.3 extracted data from UK-based studies, which were analysed to identify any additional relevant resources for use in the economic model.

5.5.1.1 Appropriateness of NHS Ref costs/ Payment by Results tariffs

In this economic analysis, the NHS reference costs, rather than Payment by Results tariffs, were used for the unit costs of managing patients while on treatment. This is a conservative approach as the NHS reference costs reflect the real cost to the service while the Payment by Results tariffs reflect how much the service is reimbursed. In addition, there is a greater level of granularity with reference costs, which allows the implementation of a more precise and detailed micro-costing approach. This approach has been adopted to be concordant with previous NICE assessments (Hartwell et al, 2011 (163), Shepherd et al, 2007 (162)).

5.5.1.2 Clinical expert assessment of applicability of cost and healthcare resource use values

Cost and resource use values in the SOF/VEL model do not differ from those employed in the previous LDV/SOF submission to NICE. Therefore, no further clinical expert input was sought on these inputs for the SOF/VEL submission. Costs were uplifted to 2014/2015 values.

5.5.2 *Intervention and comparators' costs and resource use*

5.5.2.1 Drug costs (SOF/VEL and comparators)

Unit costs of the drugs in the sofosbuvir and comparator regimens are presented in Table 83. Estimates for comparators were obtained from the British National Formulary (March 2016).

Table 83: Treatment unit costs

Drug	Cost per pack	Unit dose	Quantity/pack	Source	Assumption
SOF/VEL	£12,993.33 (Anticipated list price) [redacted]	500 mg	28	Gilead	Fixed price-CIC
LDV/SOF	£12,993.33	490 mg	28	BNF, 23rd March 2016	
SOF	£11,660.98	400 mg	28	BNF, 23rd March 2016	
RBV	£246.65	400 mg	56	BNF, 23rd March 2016	Copegus® 400mg Tablet
Peg-IFN2a	£124.40	180 µg	1	BNF, 23rd March 2016	Pegasys® Syringe
DCV	£8,172.61	60 mg	28	BNF, 23rd March 2016	Daklinza® 60mg tablets
OBV/PTV/RTV	£10,733.33	275 mg	28	BNF, 23rd March 2016	Viekirax 275mg tablets
DSV	£933.33	250 mg	56	BNF, 23rd March 2016	Exviera 250mg tablets
SMV	£1,866.50	150 mg	7	BNF, 23rd March 2016	Olysio 150mg 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

5.5.2.2 Monitoring costs

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

The unit costs used to estimate the monitoring costs are displayed in Table 84. The resource use was taken from Shepherd et al, 2007 (162) and the costs were inflated to 2014-2015 when new ones were not available.

Table 84: Monitoring resource use unit costs

Item	Unit cost	Cost year	Inflated to £2014-2015	Source

Item	Unit cost	Cost year	Inflated to £2014-2015	Source
OUTPATIENT APPOINTMENT				
Gastroenterology - Consultant Led Outpatient Attendances	£139.83	2014-2015	£139.83	National Schedule of Reference Costs Year : 2014-15 (186)
Gastroenterology - Non Consultant Led Outpatient Attendances	£97.12	2014-2015	£97.12	National Schedule of Reference Costs Year : 2014-15 (186)
INPATIENT CARE (DAY CASE)				
Clerking in patient (one hour)	£10.18	2003-2004	£13.27	Shepherd et al, 2007 (162)
TEST AND INVESTIGATIONS				
Virology				
HCV screen (RNA) = SVR test	£11.33	2003-2004	£14.77	Shepherd et al, 2007 (162)
HBV	£5.18	2003-2004	£6.75	Shepherd et al, 2007 (162)
Anti-HIV	£13.50	2011-2012	£14.01	Prof. Dusheiko
HIV RNA	£35.00	2011-2012	£36.31	Prof. Dusheiko
Chemical pathology				
Liver function tests (LFT)	£3.60	2003-2004	£4.69	Shepherd et al, 2007 (162)
Alfa-fetoprotein (AFP)	£1.31	2003-2004	£1.71	Shepherd et al, 2007 (162)
Alfa-Antitrypsin	£5.50	2003-2004	£7.17	Shepherd et al, 2007 (162)
Thyrotrophic	£3.60	2003-2004	£4.69	Shepherd et al, 2007 (162)
Free T4	£3.60	2003-2004	£4.69	Shepherd et al, 2007 (162)
Caeruloplasmin	£6.60	2003-2004	£8.61	Shepherd et al, 2007 (162)
Iron	£4.30	2003-2004	£5.61	Shepherd et al, 2007 (162)
Urea and electrolytes (U&Es)	£5.60	2003-2004	£7.30	Shepherd et al, 2007 (162)
Glucose	£2.50	2003-2004	£3.26	Shepherd et al, 2007 (162)
Pregnancy test	£0.25	2003-2004	£0.33	Shepherd et al, 2007 (162)
Thyroid function tests (TFT)	£13.30	2003-2004	£17.34	Shepherd et al, 2007 (162)
Alanine aminotransferase (Alt)	£3.60	2003-2004	£4.69	Shepherd et al, 2007 (162)
Haematology				
Full blood count (FBC)	£2.20	2003-2004	£2.87	Shepherd et al, 2007 (162)
Ferritin	£10.00	2003-2004	£13.04	Shepherd et al, 2007 (162)
Blood clotting factors (INR)	£2.40	2003-2004	£3.13	Shepherd et al, 2007 (162)
Blood group	£2.20	2003-2004	£2.87	Shepherd et al, 2007 (162)

Item	Unit cost	Cost year	Inflated to £2014-2015	Source
Immunology / chemistry				
Autoantibodies	£22.30	2003-2004	£29.08	Shepherd et al, 2007 (162)
Immunoglobulins	£2.20	2003-2004	£2.87	Shepherd et al, 2007 (162)
Cryoglobulin	£11.90	2003-2004	£15.52	Shepherd et al, 2007 (162)
Radiology				
Ultrasound scan of liver	£48.00	2003-2004	£62.58	Shepherd et al, 2007 (162)
Chest X-ray	£15.00	2003-2004	£19.56	Shepherd et al, 2007 (162)
Ultrasound guided biopsy	£173.00	2003-2004	£225.56	Shepherd et al, 2007 (162)
Ultrasound of liver	£7.20	2003-2004	£9.39	Shepherd et al, 2007 (162)
ECG	£31.00	2003-2004	£40.42	Shepherd et al, 2007 (162)
MRI liver	£206.00	2002-2003	£282.54	Wright et al, 2006 (165)
Molecular pathology				
HCV quantitative viral load	£152.27	2003-2004	£198.53	Shepherd et al, 2007 (162)
Other tests				
Pulmonary function tests	£1.00	2003-2004	£1.30	Shepherd et al, 2007 (162)
HCV genotype	£148.00	2003-2004	£192.97	Shepherd et al, 2007 (162)
Procedures				
Liver biopsy	£126.00	2003-2004	£164.28	Shepherd et al, 2007 (162)
Fibroscan	£50.00	2008-2009	£54.89	Stevenson et al 2012 (page 67) (187)
Fibrotest	£50.00	2008-2009	£54.89	Stevenson et al 2012 (page 67) (187)
Endoscopy diagnosis	£110.00	2002-2003	£150.87	Wright et al, 2006 (165)

ECG, Electrocardiography; HCV, Hepatitis C virus; kg, Kilogram; PSSRU, Personal Social Services Research Unit

Table 85 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 85: 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	-	£636
Total cirrhotic	-	£831

Further investigations for treatment group		
Total TN non-cirrhotic	-	£476
Total TN cirrhotic	-	£476
Total TE non-cirrhotic	-	£476
Total TE cirrhotic	-	£476
Monitoring during active treatment: Peg-IFN2a+RBV		
Total non-cirrhotic	4 weeks of treatment	[redacted]
	6 weeks of treatment	[redacted]
	8 weeks of treatment	[redacted]
	12 weeks of treatment	[redacted]
	16 weeks of treatment	[redacted]
	24 weeks of treatment	[redacted]
Total cirrhotic	4 weeks of treatment	[redacted]
	6 weeks of treatment	[redacted]
	8 weeks of treatment	[redacted]
	12 weeks of treatment	[redacted]
	16 weeks of treatment	[redacted]
	24 weeks of treatment	[redacted]
Supplementary monitoring for 48 weeks treatment: Peg-IFN2a+RBV		
Total non-cirrhotic	28 weeks of treatment	[redacted]
	36 weeks of treatment	[redacted]
	48 weeks of treatment	[redacted]
Total cirrhotic	28 weeks of treatment	[redacted]
	36 weeks of treatment	[redacted]
	48 weeks of treatment	[redacted]
Monitoring during active treatment: SMV+Peg-IFN2a+RBV†		
Total non-cirrhotic	4 weeks of treatment	£695
	6 weeks of treatment	£807
	8 weeks of treatment	£923
	12 weeks of treatment	£1,324
	16 weeks of treatment	£1,436
	24 weeks of treatment	£1,796
Total cirrhotic	4 weeks of treatment	£695
	6 weeks of treatment	£807
	8 weeks of treatment	£923
	12 weeks of treatment	£1,438
	16 weeks of treatment	£1,662

	24 weeks of treatment	£2,255
Supplementary monitoring for 48 weeks treatment: SMV+Peg-IFN2a+RBV‡		
Total non-cirrhotic	28 weeks of treatment	£1,964
	36 weeks of treatment	£2,208
	48 weeks of treatment	£2,680
Total cirrhotic	28 weeks of treatment	£2,423
	36 weeks of treatment	£2,781
	48 weeks of treatment	£3,749
Monitoring during active treatment: All other treatments		
Total non-cirrhotic	4 weeks of treatment	£598
	6 weeks of treatment (excl. final visit)	£598
	6 weeks of treatment (incl. final visit)	£987
	8 weeks of treatment (excl. final visit)	£710
	8 weeks of treatment (incl. final visit)	£987
	12 weeks of treatment (excl. final visit)	£822
	12 weeks of treatment (incl. final visit)	£1,099
	16 weeks of treatment (excl. final visit)	£934
	16 weeks of treatment (incl. final visit)	£1,211
	24 weeks of treatment	£1,323
Total cirrhotic	4 weeks of treatment	£598
	6 weeks of treatment (excl. final visit)	£598
	6 weeks of treatment (incl. final visit)	£988
	8 weeks of treatment (excl. final visit)	£710
	8 weeks of treatment (incl. final visit)	£988
	12 weeks of treatment (excl. final visit)	£822
	12 weeks of treatment (incl. final visit)	£1,100
	16 weeks of treatment (excl. final visit)	£934
	16 weeks of treatment (incl. final visit)	£1,212
	24 weeks of treatment	£1,324
Surveillance of patients who are unsuitable to Peg-IFN (per year)		
Total non-cirrhotic	1 year	£107
Total cirrhotic	1 year	£338

Peg-IFN2a, Pegylated interferon alfa-2a; RBV, Ribavirin; SMV, Simeprevir; TE, Treatment-experienced; TN, Treatment-naïve; wks, Weeks;
† 50% of patients have 2 extra-visits (assumed in week 9 and 23); ‡ 50% of patients have 2 extra-visits (assumed in week 26 and 47).

5.5.3 *Health-state costs and resource use*

Costs associated with each health state are shown in Table 86. 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 (165). 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 (188). 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 (188) 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 (165). Costs of non-cirrhotic and cirrhotic patients who reached SVR were from Grishchenko et al, 2009 (164) because the costs collected from the UK mild hepatitis C RCT (which were used by Shepherd et al, 2007 (162) and Hartwell et al, 2011 (163)) did not split between non-cirrhotic and cirrhotic patients. Costs of decompensated cirrhosis with SVR were conservatively assumed to be the same as those without SVR. All costs have been updated to 2014/2015 costs using the HCHS Pay and Prices Index (189).

Table 86: Health state costs

Health state ***Disaggregated costs***	**Annual costs**	**Cost year**	**Inflated-values to £2014-2015**	**Source**
Non-cirrhotic, mild	£138	2002-2003	£189	Wright et al, 2006 (165)
Non-cirrhotic, moderate	£730	2002-2003	£1,001	Wright et al, 2006 (165)
Non-cirrhotic†	-	-	£327	Calculation
Non-cirrhotic with SVR (mild)	£202	2006-2007	£237	Grishchenko et al, 2009 (164)
Non-cirrhotic with SVR (moderate)	£247	2006-2007	£290	Grishchenko et al, 2009 (164)
Non-cirrhotic with SVR†	-	-	£246	Calculation
Compensated cirrhosis	£1,138	2002-2003	£1,561	Wright et al, 2006 (165)

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

Health state *Disaggregated costs*	Annual costs	Cost year	Inflated-values to £2014-2015	Source
Pharmacy			£390	Calculation (Total costs divided by 4)
Hospitalisation			£390	Calculation (Total costs divided by 4)
Outpatient‡			£780	Calculation (sum of emergency and ambulatory costs)
Emergency			£390	Calculation (Total costs divided by 4)
Ambulatory			£390	Calculation (Total costs divided by 4)
Compensated cirrhosis with SVR	£437	2006-2007	£513	Grishchenko et al, 2009 (164)
Pharmacy			£128	Calculation (Total costs divided by 4)
Hospitalisation			£128	Calculation (Total costs divided by 4)
Outpatient‡			£256	Calculation (sum of emergency and ambulatory costs)
Emergency			£128	Calculation (Total costs divided by 4)
Ambulatory			£128	Calculation (Total costs divided by 4)
Decompensated cirrhosis	£9,121	2002-2003	£12,510	Wright et al, 2006 (165)
Pharmacy			£3,127	Calculation (Total costs divided by 4)
Hospitalisation			£3,127	Calculation (Total costs divided by 4)
Outpatient‡			£6,255	Calculation (sum of emergency and ambulatory costs)
Emergency			£3,127	Calculation (Total costs divided by 4)
Ambulatory			£3,127	Calculation (Total costs divided by 4)
Decompensated cirrhosis with SVR	£9,121	2002-2003	£12,510	Assumed same as decompensated cirrhosis from Wright et al, 2006 (165)
Pharmacy			£3,127	Calculation (Total costs divided by 4)
Hospitalisation			£3,127	Calculation (Total costs divided by 4)
Outpatient‡			£6,255	Calculation (sum of emergency and ambulatory costs)
Emergency			£3,127	Calculation (Total costs divided by 4)
Ambulatory			£3,127	Calculation (Total costs divided by 4)
HCC	£8,127	2002-2003	£11,147	Wright et al, 2006 (165)
Pharmacy			£2,787	Calculation (Total costs divided by 4)
Hospitalisation			£2,787	Calculation (Total costs divided by 4)
Outpatient‡			£5,573	Calculation (sum of emergency and ambulatory costs)
Emergency			£2,787	Calculation (Total costs divided by 4)
Ambulatory			£2,787	Calculation (Total costs divided by 4)
Liver transplant	£83,505	2012-2013	£85,191	Longworth et al 2014 (188)
Pharmacy			£21,298	Calculation (Total costs divided by 4)
Hospitalisation			£21,298	Calculation (Total costs divided by 4)
Outpatient‡			£42,595	Calculation (sum of emergency and

Health state *Disaggregated costs*	Annual costs	Cost year	Inflated-values to £2014-2015	Source
				ambulatory costs)
Emergency			£21,298	Calculation (Total costs divided by 4)
Ambulatory			£21,298	Calculation (Total costs divided by 4)
Post-liver transplant follow-up phase (0-12 months)	£27,512	2012-2013	£28,067	Longworth et al 2014 (188); Split between post-liver transplant year 1 and year 2 cost based on Wright et al 2006 (165)
Post-liver transplant follow-up phase (12-24 months)	£4,111	2012-2013	£4,194	

HCC, Hepatocellular carcinoma; SVR, Sustained virologic response;
† 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; ‡Outpatient costs are the sums of emergency and ambulatory costs.

5.5.4 *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 87 and Table 88.

Data were obtained from the BNF March 2016 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 (162). Outpatient, GP and specialist costs are shown in Table 89.

Table 87: Adverse event drug unit costs

Adverse event	Drug	Cost per pack	Unit dose	Quantity/ pack	Source
Nausea	Metoclopramide	£0.83	10 mg	28	BNF, 23rd March 2016
Vomiting	Metoclopramide	£0.83	10 mg	28	BNF, 23rd March 2016
Diarrhoea	Loperamide	£1.83	2 mg	30	BNF, 23rd March 2016
Pruritus	Chlorphenamine	£0.84	4 mg	28	BNF, 23rd March 2016
Rash	Hydrocortisone 1% 15g	£1.25	NA	1	BNF, 23rd March 2016; Hydrocortisone 1% ointment 15g
Anaemia (Epo)	Binocrit® (epoetin alfa)	£43.27	10,000 units	1	BNF, 23rd March 2016; Prefilled syringe
Anaemia (blood transfusion)	NA	£1,037.10	NA	1	National Schedule of Reference Costs - Year 2014-15 - 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) (186)
Thrombocytopenia	Revolade®	£1,540.00	50 mg	28	BNF, 23rd March 2016

Adverse event	Drug	Cost per pack	Unit dose	Quantity/ pack	Source
	(eltrombopag)				
Neutropenia	Neupogen® (filgrastim)	£52.70	600 µg/ml	0.5	BNF, 23rd March 2016; Singleject® 0.5-ml prefilled syringe
Depression	Citalopram	£1.02	20 mg	28	BNF, 23rd March 2016; NICE guidance CG91 Depression with a chronic physical health problem

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

Table 88: 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%	£0.62	4	Telaprevir manufacturer's submission to NICE (TA252)
Vomiting	Metoclopramide	30 mg/day	100%	£0.62	4	Telaprevir manufacturer's submission to NICE (TA252)
Diarrhoea	Loperamide	2 mg/day	100%	£0.43	4.3	Telaprevir manufacturer's submission to NICE (TA252)
Pruritus	Chlorphenamine	16 mg/day	100%	£0.84	4	Telaprevir manufacturer's submission to NICE (TA252)
Rash	Hydrocortisone 1% 15g	NA	100%	£0.31	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%	£1.73	4	Gao et al, 2012 (190); Assumption: 4-week treatment; % patients treated based on the average of three HCV centres in the UK
Anaemia (blood transfusion)†	NA	1	0.7%	£7.26	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, 23rd March 2016; Assumption:

Adverse event	Drug	Dose	% treated for	Weekly costs	Weeks of treatment	Source
						4-week treatment
Neutropenia	Neupogen® (filgrastim)	395 µg/d = 5*79	100%	£485.72	2	BNF, 23rd March 2016
Depression	Citalopram	20 mg/d	100%	£0.26	4	BNF, 23rd March 2016; Assumption: 4-week treatment

BNF, British National Formulary; epo, erythropoietin; NA, not applicable; NICE, National Institute for Health and Care Excellence; wk, week.
† HRG "Single Plasma Exchange, Leukapheresis or Red Cell Exchange, with length of stay 2 days or less, 19 years and over".

Table 89: 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	£41.00	£164.00	KOL Opinion; PSSRU unit costs 2015 - Hospital, day ward; Each visit is assumed to take 1 hour (189)
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	100%	2	£223.35	£446.70	KOL Opinion; National Schedule of Reference Costs Year 2014-15 - Consultant-led costs for Hepatology (186)
Anaemia (Epo)	Outpatient	100%	6	£41.00	£2.46	KOL Opinion; PSSRU unit costs 2015 - Hospital, day ward; Each visit is assumed to take 1 hour (189)

Adverse event	Items	% of patients	Units	Cost	Total cost (for % who receive treatment)	Source
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	50%	1	£223.35	£1.12	KOL Opinion; National Schedule of Reference Costs Year 2014-15 - Consultant-led costs for Hepatology (186)
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	£223.35	£0.78	KOL Opinion; National Schedule of Reference Costs Year 2014-15 - Consultant-led costs for Hepatology (186)
Thrombocytopenia	Outpatient	100%	6	£41.00	£246.00	KOL Opinion; PSSRU unit costs 2015 - Hospital, day ward; Each visit is assumed to take 1 hour (189)
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	50%	1	£223.35	£111.67	KOL Opinion; National Schedule of Reference Costs Year 2014-15 - Consultant-led costs for Hepatology (186)
Neutropenia	Outpatient	100%	6	£41.00	£246.00	KOL Opinion; PSSRU unit costs 2015 - Hospital, day ward; Each visit is assumed to take 1 hour (189)
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	50%	1	£223.35	£111.67	KOL Opinion; National Schedule of Reference Costs Year 2014-15 - Consultant-led costs for Hepatology (186)

Adverse event	Items	% of patients	Units	Cost	Total cost (for % who receive treatment)	Source
Depression	Outpatient	0%	0	£0.00	£0.00	KOL Opinion
	GP	100%	8	£13.67	£109.33	KOL Opinion; PSSRU unit costs 2015 - Registrar group; £41 per hour; Each visit is assumed to take 20 minutes (189)
	Specialist	0%	0	£0.00	£0.00	KOL Opinion

GP, General practitioner; HRG, healthcare resource group; KOL, Key opinion leader.

5.5.5 *Miscellaneous unit costs and resource use*

Not applicable

5.6 *Summary of base-case de novo analysis inputs and assumptions*

5.6.1 *Summary of base-case de novo analysis inputs*

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

- Patient characteristics – Table 79
- TPs – Table 81
- Health state HRQL – Table 82
- Costs – Section 5.5

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

- SVRs
- Treatment duration
- Treatment-related adverse events
- Treatment specific quality of life
    - The utility decrements are expressed as a percentage due to using a multiplicative approach

5.6.1.1 GT3 TN

SVR

Table 90: GT3 TN: SVR

Strategy	Initial state	SVR % (n/N)	Source
Sofosbuvir/velpatasvir (12 wks)	Non-cirrhotic	98.2% (160/163)	ASTRAL-3 (28)
	Cirrhotic	93.0% (40/43)	ASTRAL-3 (28)
Sofosbuvir + RBV (24 wks)	Non-cirrhotic	90.4% (141/156)	ASTRAL-3 (28)
	Cirrhotic	73.3% (33/45)	ASTRAL-3 (28)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	Non-cirrhotic	95.8% (68/71)	BOSON trial (86)
	Cirrhotic	91.3% (21/23)	BOSON trial (86)
Sofosbuvir + daclatasvir + RBV (24 wks)	Non-cirrhotic	NA	NA
	Cirrhotic	57.9% (11/19)	No data is available for SOF+DCV+RBV 24 weeks. As a proxy, data for SOF+DCV 12 weeks is used from ALLY-3 (Fig 2A) (150) as presented in Table 3 of NICE TA364, for patients with cirrhosis (56)
Sofosbuvir + daclatasvir (12 wks)	Non-cirrhotic	77.8% (28/36)	ALLY-3 (Fig 2A) (150); data as presented in Table 3 of NICE TA364 for F3/F4 (56)
	Cirrhotic	NA	NA
Peg-IFN2a + RBV (24 wks)	Non-cirrhotic	71.2% (99/139)	Sovaldi SmPC FISSION (191)
	Cirrhotic	29.7% (11/37)	Sovaldi SmPC FISSION (191)

Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; SVR, Sustained virologic response; TE, Treatment-experienced; TN, Treatment-naïve; wks, weeks

Treatment duration

Table 91: GT3 TN: treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir/velpatasvir (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	ASTRAL-3 (28)

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir + RBV (24 wks)	98.4% (246/250)	24.0	0.4% (1/250)	21.5	1.2%	21.5	VALENCE (149); 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
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	BOSON trial (86)
Sofosbuvir + daclatasvir + RBV (24 wks)							No data available; As a proxy, data for SOF+DCV 12 weeks is used from ALLY-3 below
Sofosbuvir + daclatasvir (12 wks)	99.0% (100/101)	12.0	0.0%	0.0	1.0%	8.0	ALLY-3 (150)
Peg-IFN2a + RBV (24 wks)	76.1% (134/176)	24.0	10.2% (18/176)	10.8	13.6%	11.9	Assumed equal to 12 weeks from FISSION (19)
No treatment	0.0%	0.0	0.0%	0.0	100.0%	0.0	No treatment

AE, Adverse event; CSR, Clinical study report; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TN, Treatment-naive; wks, Weeks.
† Calculated as 100%-sum of the other categories

Treatment-related adverse events

Table 92: GT3 TN: Treatment safety

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir/velpatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ASTRAL-3 (28)
Sofosbuvir + RBV (24 wks)	0.0%	0.4% (1/250)	0.0%	0.0%	0.0%	0.8% (2/250)	0.8% (2/250)	0.0%	0.0%	0.0%	0.0%	VALENCE (149)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	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

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
												(19)
Sofosbuvir + daclatasvir + RBV (24 wks)												No data available; As a proxy, data for SOF+DCV 12 weeks is used from ALLY-3 below
Sofosbuvir + daclatasvir (12 wks)	0.7% (1/152)	0.7% (1/152)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ALLY-3 (150)
Peg-IFN2a + RBV (24 wks)	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 (19)

AE, Adverse event; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TN, Treatment-naïve; wks, weeks

Treatment-specific quality of life

Table 93: GT3 TN: Treatment-specific quality of life

Strategy	Utility increment/decrement	Source
Sofosbuvir/velpatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Sofosbuvir + RBV (24 wks)	-2.55%	FISSION (19)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	-14.52%	Assumed equal to NEUTRINO (19)
Sofosbuvir + daclatasvir + RBV (24 wks)	-3.25%	Assumed equal to ION trials for LDV/SOF + RBV (12 wks)
Sofosbuvir + daclatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Peg-IFN2a + RBV (24 wks)	-14.77%	Wright, 2006 (UK mild HCV trial) (165)

GT, Genotype; HCV, Hepatitis C virus; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TN, Treatment-naive; wks, weeks

5.6.1.2 GT3 TE

SVR

Table 94: GT3 TE: SVR

Strategy	Initial state	SVR % (n/N)	Source
Sofosbuvir/velpatasvir (12 wks)	Non-cirrhotic	91.2% (31/34)	ASTRAL-3 (28)
	Cirrhotic	89.2% (33/37)	ASTRAL-3 (28)
Sofosbuvir + RBV (24 wks)	Non-cirrhotic	71.0% (22/31)	ASTRAL-3 (28)
	Cirrhotic	57.9% (22/38)	ASTRAL-3 (28)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	Non-cirrhotic	94.2% (49/52)	BOSON trial (86)
	Cirrhotic	85.7% (30/35)	BOSON trial (86)
Sofosbuvir + daclatasvir + RBV (24 wks)	Non-cirrhotic	NA	NA
	Cirrhotic	69.2% (9/13)	No data is available for SOF+DCV+RBV 24 weeks. As a proxy, data for SOF+DCV 12 weeks is used from ALLY-3 (Fig 2A) (150) as presented in Table 3 of NICE TA364 for patients with cirrhosis (56))
Sofosbuvir + daclatasvir (12 wks)	Non-cirrhotic	71.4% (15/21)	ALLY-3 (150); data as presented in Table 3 of NICE TA364 for F3/F4 (56))
	Cirrhotic	NA	NA
Peg-IFN2a + RBV (48 wks)	Non-cirrhotic	35.0% (0.625*0.53+0.375*0.05)	Lagging et al (151) And Shoeb et al (192)†
	Cirrhotic	35.0% (0.625*0.53+0.375*0.05)	Lagging et al (151) And Shoeb et al (192)†

Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; SVR, Sustained virologic response; TE, Treatment-experienced; wks, Weeks
† SVRs are for GT2 and GT3 combined (in Lagging these corresponded to 18% and 82%, respectively); data is for non-cirrhotic and cirrhotic combined as no split was provided

Treatment duration

Table 95: GT3 TE: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir/velpatasvir (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	ASTRAL-3 (28)

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir + RBV (24 wks)	98.4% (246/250)	24.0	0.4% (1/250)	21.5	1.2%	21.5	VALENCE (149)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	99.0% (102/103)	12.0	1.0% (1/103)	1.0	0.0%	0.0	BOSON trial (86)
Sofosbuvir + daclatasvir + RBV (24 wks)							No data available; As a proxy, data for SOF+DCV 12 weeks is used from ALLY-3 below
Sofosbuvir + daclatasvir (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0	ALLY-3 (150)
Peg-IFN2a + RBV (24 wks)	63.2% (1-14/38)	48.0	36.8% (14/38)	24.0	0.0%	0.0	Lagging (2013) (151) (Number of weeks for discontinuations is an assumption)

AE, Adverse event; CSR, Clinical study report; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TN, Treatment-naive; wks, Weeks
† Calculated as 100%-sum of the other categories

Treatment-related adverse events

Table 96: GT3 TE: Treatment safety

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir/velpatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ASTRAL-3 (28)
Sofosbuvir + RBV (24 wks)	0.0%	0.4% (1/250)	0.0%	0.0%	0.0%	0.8% (2/250)	0.8% (2/250)	0.0%	0.0%	0.0%	0.0%	VALENCE (149)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	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 (19)
Sofosbuvir + daclatasvir+ RBV (24 wks)												No data available; As a proxy, data for SOF+DCV 12 weeks is used from

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
												ALLY-3 below
Sofosbuvir + daclatasvir + (12 wks)	0.7% (1/152)	0.7% (1/152)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ALLY-3 (150)
Peg-IFN2a + RBV (24 wks)	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 (19)

AE, Adverse event; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TE, Treatment-experienced; wks, weeks

Treatment-specific quality of life

Table 97: GT3 TE: Treatment-specific quality of life

Strategy	Utility increment/decrement	Source
Sofosbuvir/velpatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Sofosbuvir + RBV (24 wks)	-6.88%	FISSION (19)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	-14.52%	Assumed equal to NEUTRINO (19)
Sofosbuvir + daclatasvir + RBV (24 wks)	-1.00%	Assumed equal to ION trials for LDV/SOF + RBV (24 wks)
Sofosbuvir + daclatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Peg-IFN2a + RBV (24 wks)	-14.77%	Wright, 2006 (UK mild HCV trial) (165)

5.6.1.3 GT1 (1, 1a, 1b) TN

SVR

Table 98: GT1/1a/1b TN: SVR

Strategy	Initial state	GT1	GT1a		GT1b	
		SVR %	SVR % (n/N)	Source	SVR % (n/N)	Source
Sofosbuvir/velpatasvir (12 wks)	Non-cirrhotic	98.4%	97.5% (157/161)	ASTRAL-1 (SVR by cirrhotic stage - no distinction between TN and TE) (70)	100.0% (94/94)	ASTRAL-1 (SVR by cirrhotic stage - no distinction between TN and TE) (70)

Strategy	Initial state	GT1	GT1a		GT1b	
		SVR %	SVR % (n/N)	Source	SVR % (n/N)	Source
	Cirrhotic	98.5%	100.0%	ASTRAL-1 (SVR by cirrhotic stage - no distinction between TN and TE) (70)	95.8% (23/24)	ASTRAL-1 (SVR by cirrhotic stage - no distinction between TN and TE) (70)
Ledipasvir/sofosbuvir (8 wks)	Non-cirrhotic	94.0%	94.0% (202/215)	ION-3 all GT1 patients ((27) and SmPC)	94.0% (202/215)	ION-3 all GT1 patients ((27) and SmPC)
	Cirrhotic	NA	NA	NA	NA	NA
Ledipasvir/sofosbuvir (12 wks)	Non-cirrhotic	NA	NA	NA	NA	NA
	Cirrhotic	94.1%	94.1% (32/34)	ION-1 GT 1a/b mixed ((101) and SmPC)	94.1% (32/34)	ION-1 GT 1a/b mixed ((101) and SmPC)
Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)	Non-cirrhotic	NA	NA	NA	99.0% (207/209)	PEARL-III (112)
	Cirrhotic	NA	NA	NA	NA	NA
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	Non-cirrhotic	NA	97.0% (97/100)	PEARL-IV (112)	NA	NA
	Cirrhotic	100.0%	NA	NA	100.0% (22/22)	TURQUOISE-II (137)
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	Non-cirrhotic	NA	NA	NA	NA	NA
	Cirrhotic	95.4%	92.9% (52/56)	TURQUOISE-II (137)	NA	NA
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	Non-cirrhotic	91.7%	91.7% (220/240)	NEUTRINO (19)	91.7% (220/240)	NEUTRINO (19)
	Cirrhotic	80.8%	80.8% (42/52)	NEUTRINO (19)	80.8% (42/52)	NEUTRINO (19)
Sofosbuvir + daclatasvir (12 wks)	Non-cirrhotic	100.0%	100.0% (15+19)/(15+19)	Sulkowski et al (AI444040 study group) (81); data as presented in Table 3 of NICE TA364 for F3/F4 (56))	100.0% (15+19)/(15+19)	Sulkowski et al (AI444040 study group) (81); data as presented in Table 3 of NICE TA364 for F3/F4 (56))
	Cirrhotic	NA	NA	NA	NA	NA
Sofosbuvir + daclatasvir + RBV (24 wks)	Non-cirrhotic	NA	NA	NA	NA	NA
	Cirrhotic	100.0%	100.0% (14/14)	ANRS CO22 HEPATHER (Pol 2015 EASL) (153); data are SVR4 for all TN patients (NC+CC)	100.0% (14/14)	ANRS CO22 HEPATHER (Pol 2015 EASL) (153); data are SVR4 for all TN patients (NC+CC)

Strategy	Initial state	GT1	GT1a		GT1b	
		SVR %	SVR % (n/N)	Source	SVR % (n/N)	Source
Simeprevir + Peg-IFN2a + RBV (RGT)	Non-cirrhotic	82.0%	82.0% (317+89-29)/(2378+130-48)	Olysio SmPC (pooled data from C208 and C216)	82.0% (317+89-29)/(2378+130-48)	Olysio SmPC (pooled data from C208 and C216)
	Cirrhotic	60.4%	60.4% (29/48)	Olysio SmPC (pooled data from C208 and C216)	60.4% (29/48)	Olysio SmPC (pooled data from C208 and C216)
Peg-IFN2a + RBV (48 wks)	Non-cirrhotic	43.6%	43.6% (376/862)	McHutchison 2009 (F0-F2) (154)	43.6% (376/862)	McHutchison 2009 (F0-F2) (154)
	Cirrhotic	23.6%	23.6% (26/110)	McHutchison 2009 (F3-F4) (154)	23.6% (26/110)	McHutchison 2009 (F3-F4) (154)

CC, compensated cirrhosis; GT, genotype; NA, Not applicable; NC, non-cirrhotic; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; RGT, Response Guided Therapy; SmPC, Summary of product characteristics; SVR, Sustained

Treatment duration

Table 99: GT1/1a/1b TN non-cirrhotic: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir/velpatasvir (12 wks)	99.7% (327/328)	12.0	0.3% (1/328)	2.0	0.0%	0.0	ASTRAL-1 (one GT1a non-cirrhotic patient discontinued at day 13, treatment history of this patient is not available) (70)
Ledipasvir/sofosbuvir (8 wks)	100.0%	8.0	0.0%	0.0	0.0%	0.0	ION-3 (journal supplementary materials) (27)
Ledipasvir/sofosbuvir (12 wks)	99.1% (212/214)	12.0	0.0%	0.0	0.9%	6.0	ION-1 (101) (CSR)‡
Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)	97.1% (208+194)/(209+205)	12.0	0.5% (2+0))/(205+209)	6.0	2.4%	6.0	PEARL-III and PEARL-IV‡ (112)
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	99.7% (209+100)/(210+100)	12.0	0.0% (0+0)/(210+100)	6.0	0.3%	6.0	PEARL-III and PEARL-IV‡ (112)

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	97.6% (285/292)	12.0	1.7% (5/292)	5.3	0.7%	4.8	NEUTRINO (19)
Sofosbuvir + daclatasvir (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	Sulkowski et al (AI444040 study group) (81)
Simeprevir + Peg-IFN2a + RBV (RGT)	93.3% (729/781)	12.0 24.0	1.8% (14/781)	12.0	4.9%	12.0	According to 2015 EASL guidelines, SMV should be administered for 12 weeks with PR. PR should then be administered alone for an additional 12 wks for treatment-naïve - Pooling QUEST1/2 (120, 121) + PROMISE (115)‡
Peg-IFN2a + RBV (48 wks)	60.0%	48.0	13.0%	24.0	27.0%	24.0	McHutchison (2009)‡ (154)

AE, Adverse Events; EASL, European Association for the Study of Liver; GT, Genotype; Peg-IFN2a, Pegylated interferon alfa-2a; RBV, Ribavirin; RGT, Response Guided Therapy; TE, Treatment experienced; TN, Treatment naïve; wks, weeks;
† Calculated as 100%-sum of the other categories
‡ Number of weeks for discontinuation due to AEs is an assumption

Table 100: GT1/1a/1b TN cirrhotic: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir/velpatasvir (12 wks)	99.7% (327/328)	12.00	0.3% (1/328)	2.00	0.0%	0.00	ASTRAL-1 (one GT1a non-cirrhotic patient discontinued at day 13, treatment history of this patient is not available) (70)
Ledipasvir/sofosbuvir (12 wks)	99.1% (212/214)	12.00	0.0%	0.00	0.9%	6.00	ION-1 (101) (CSR)‡
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	98.1% (204/208)	12.00	1.9% (4/208)	6.00	0.0%	6.00	TURQUOISE-II‡ (137)
Ombitasvir/paritaprevir/ritonavir +	94.8%	24.00	2.3% (4/172)	12.00	2.9%	12.00	TURQUOISE-II‡ (137)

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
dasabuvir + RBV (24 wks)	(163/172)						
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	97.6% (285/292)	12.00	1.7% (5/292)	5.30	0.7%	4.80	NEUTRINO (19)
Sofosbuvir + daclatasvir + RBV (24 wks) Data assumed to be equivalent to sofosbuvir + daclatasvir (12 wks)	100.0%	12.00	0.0%	0.00	0.0%	0.00	Sulkowski et al (AI444040 study group) (81)
Simeprevir + Peg-IFN2a + RBV (RGT)	93.3% (729/781)	24.00	1.8% (14/781)	12.00	4.9%	12.00	According to 2015 EASL guidelines, SMV should be administered for 12 weeks with PR. PR should then be administered alone for an additional 12 wks for treatment-naïve - Pooling QUEST1/2 (120, 121) + PROMISE (115)‡
Peg-IFN2a + RBV (48 wks)	60.0%	48.00	13.0%	24.00	27.0%	24.00	McHutchison (2009)‡ (154)

Treatment experienced; TN, Treatment naïve; wks, weeks;
† Calculated as 100%-sum of the other categories
‡ Number of weeks for discontinuation due to AEs is an assumption

Treatment-related adverse events

Table 101: GT1/1a/1b TN non-cirrhotic: Treatment safety

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir/velpatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ASTRAL-1 (70)
Ledipasvir/sofosbuvir (8 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ION-3 (CSR - Table 11-4) (27)

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Ledipasvir/sofosbuvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ION-1 (CSR - Table 11-4) (101)
Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Assumption
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Assumption
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	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%	NEUTRINO (19)
Sofosbuvir + daclatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Sulkowski et al (AI444040 study group) - Supplementary materials (one G3/4 AE occurred = psoriasis) (ulkowski et al (AI444040 study group) - Supplementary materials (one G3/4 AE occurred = psoriasis)) (81)
Simeprevir + Peg-IFN2a + RBV (RGT)	0.0%	0.0%	0.0%	0.1% (1/718)	0.3% (2/718)	1.0%	1.0%	0.0%	10.0%	0.0%	0.0%	Pooling QUEST1/2 (120, 121) + PROMISE (115) (Antiviral Drugs Advisory Committee Meeting - Janssen -2013 -Table 24-27)
Peg-IFN2a + RBV (48 wks)	1.0%	0.0%	0.0%	0.1%	0.1%	24.9% (5+85)/(21+340)	24.9% (5+85)/(21+340)	0.6% (0+1+1+0)/(21+340)	14.7% (4+0+39+10)/(21+340)	0.3%	0.0%	Anaemia/neutropenia/thrombocytopenia : Kauffman et al (2011) (ADVANCE trial) (193); Other: FDA; 0% assumed for severe liver injury

Table 102: GT1/1a/1b TN cirrhotic: Treatment safety

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir/velpatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ASTRAL-1 (70)
Ledipasvir/sofosbuvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ION-1 (CSR - Table 11-4) (101)
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Assumption
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Assumption
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	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%	NEUTRINO (19)
Sofosbuvir + daclatasvir + RBV (24 wks) Data assumed to be equivalent to sofosbuvir + daclatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Sulkowski et al (AI444040 study group) - Supplementary materials (one G3/4 AE occurred = psoriasis) (ulkowski et al (AI444040 study group) - Supplementary materials (one G3/4 AE occurred = psoriasis)) (81)
Simeprevir + Peg-IFN2a + RBV (RGT)	0.0%	0.0%	0.0%	0.1% (1/718)	0.3% (2/718)	1.0%	1.0%	0.0%	10.0%	0.0%	0.0%	Pooling QUEST1/2 (120, 121) + PROMISE (115) (Antiviral Drugs Advisory Committee Meeting - Janssen -2013 -Table 24-27)
Peg-IFN2a + RBV (48 wks)	1.0%	0.0%	0.0%	0.1%	0.1%	24.9% (5+85)/(21+340)	24.9% (5+85)/(21+340)	0.6% (0+1+1+0)/(21+340)	14.7% (4+0+39+10)/(21+340)	0.3%	0.0%	Anaemia/neutropenia/thrombocytopenia : Kauffman et al (2011) (ADVANCE trial) (193); Other: FDA; 0% assumed for severe

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
												liver injury

Treatment-specific quality of life

Table 103: GT1/1a/1b TN non-cirrhotic: Treatment-specific quality of life

Strategy	Utility increment/decrement	Source
Sofosbuvir/velpatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Ledipasvir/sofosbuvir (8 wks)	4.43%	ION trials (LDV/SOF 12 wks) (27, 101, 102)
Ledipasvir/sofosbuvir (12 wks)	4.43%	ION trials (LDV/SOF 12 wks) (27, 101, 102)
Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	-3.25%	Assumed equal to ION trials for LDV/SOF + RBV (12 wks)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	-14.52%	NEUTRINO (19)
Sofosbuvir + daclatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Simeprevir + Peg-IFN2a + RBV (RGT)	-14.27%	Assumed equal to telaprevir (NICE TA252 (ADVANCE trial))
Peg-IFN2a + RBV (48 wks)	-14.77%	Wright, 2006 (UK mild HCV trial) (167)

GT, Genotype; Peg-IFN2a, Pegylated interferon alfa-2a; RBV, Ribavirin; wks, Weeks

Table 104: GT1/1a/1b TN cirrhotic: Treatment-specific quality of life

Strategy	Utility increment/decrement	Source
Sofosbuvir/velpatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Ledipasvir/sofosbuvir (12 wks)	4.43%	ION trials (LDV/SOF 12 wks) (27, 101, 102)
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	-3.25%	Assumed equal to ION trials for LDV/SOF + RBV (12 wks)
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	-1.00%	Assumed equal to ION trials for LDV/SOF + RBV (24 wks)

Strategy	Utility increment/decrement	Source
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	-14.52%	NEUTRINO (19)
Sofosbuvir + daclatasvir + RBV (24 wks) Data assumed to be equivalent to sofosbuvir + daclatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Simeprevir + Peg-IFN2a + RBV (RGT)	-14.27%	Assumed equal to telaprevir (NICE TA252 (ADVANCE trial))
Peg-IFN2a + RBV (48 wks)	-14.77%	Wright, 2006 (UK mild HCV trial) (165)

GT, Genotype; Peg-IFN2a, Pegylated interferon alfa-2a; RBV, Ribavirin; wks: Weeks

5.6.1.4 GT1 (1, 1a, 1b) TE

SVR

Table 105: GT1/1a/1b TE: SVR

Strategy	Initial state	GT1	GT1a		GT1b	
		SVR % (n/N)	SVR % (n/N)	Source	SVR % (n/N)	Source
Sofosbuvir/velpatasvir (12 wks)	Non-cirrhotic	98.4%	97.5% (157/161)	ASTRAL-1 (SVR by cirrhotic stage - no distinction between TN and TE) (70)	100.0% (94/94)	ASTRAL-1 (70)
	Cirrhotic	98.5%	100.0% (49/49)	ASTRAL-1 (SVR by cirrhotic stage - no distinction between TN and TE) (70)	95.8% (23/24)	ASTRAL-1 (70)
Ledipasvir/sofosbuvir (12 wks)	Non-cirrhotic	95.4%	95.4% (83/87)	ION-2 ((102) and SmPC)	95.4% (83/87)	ION-2 ((102) and SmPC)
	Cirrhotic	86.4%	86.4% (19/22)	ION-2 ((102) and SmPC)	86.4% (19/22)	ION-2 ((102) and SmPC)
Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)	Non-cirrhotic	NA	NA	NA	100% (91/91)	PEARL-II (111)
	Cirrhotic	NA	NA	NA	NA	NA
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	Non-cirrhotic	NA	96.0% (166/173)	SAPPHIRE-II (126)	NA	NA
	Cirrhotic	NA	NA	NA	97.8% (25+6+14)/(25+7+14)	TURQUOISE-II (137)

Strategy	Initial state	GT1	GT1a		GT1b	
		SVR % (n/N)	SVR % (n/N)	Source	SVR % (n/N)	Source
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	Non-cirrhotic	NA	NA	NA	NA	NA
	Cirrhotic	NA	95.4% (39+10+13)/(42+10+13)	TURQUOISE-II (137)	NA	NA
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	Non-cirrhotic	74.0%	74.0% (37/50)	FDA bridging analysis	74.0% (37/50)	FDA bridging analysis
	Cirrhotic	74.0%	74.0% (37/50)	FDA bridging analysis	74.0% (37/50)	FDA bridging analysis
Sofosbuvir + daclatasvir (12 wks)	Non-cirrhotic	100.0%	100.0% (21/21)	Sulkowski et al (AI444040 study group) (81); data as presented in Table 3 of NICE TA364 for F3/F4 (56))	100.0% (21/21)	Sulkowski et al (AI444040 study group) (81); data as presented in Table 3 of NICE TA364 for F3/F4 (56))
	Cirrhotic	NA	NA	NA	NA	NA
Sofosbuvir + daclatasvir + RBV (24 wks)	Non-cirrhotic	NA	NA	NA	NA	NA
	Cirrhotic	100%	98.5% (65/66)	ANRS CO22 HEPATHER (Pol 2015 EASL) (153) (153); data are SVR4 for all TE patients (NC+CC)	98.5% (65/66)	ANRS CO22 HEPATHER (Pol 2015 EASL) (153) (153); data are SVR4 for all TE patients (NC+CC)
Simeprevir + Peg-IFN2a + RBV (RGT)	Non-cirrhotic	80.1%	80.1% (137+61-29)/(167+83-39)	Olysio SmPC (pooled data from C208 and C216)	80.1% (137+61-29)/(167+83-39)	Olysio SmPC (pooled data from C208 and C216)
	Cirrhotic	74.4%	74.4% (29/39)	Olysio SmPC (pooled data from C208 and C216)	74.4% (29/39)	Olysio SmPC (pooled data from C208 and C216)
Peg-IFN2a + RBV (48 wks)	Non-cirrhotic	17.6%	17.6% (12+2+3+0+1+0)/(38+15+17+5+18+9)	Telaprevir SmPC (REALIZE) - Table 12 (2015) (194)	17.6% (12+2+3+0+1+0)/(38+15+17+5+18+9)	Telaprevir SmPC (REALIZE) - Table 12 (2015) (194)
	Cirrhotic	10.0%	10.0% (1+1+1)/(15+5+10)	Telaprevir SmPC (REALIZE) - Table 12 (2015) (194)	10.0% (1+1+1)/(15+5+10)	Telaprevir SmPC (REALIZE) - Table 12 (2015) (194)

CC, compensated cirrhosis; GT: genotype; NA, Not applicable; NC, non-cirrhotic; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; RGT, Response Guided Therapy; SmPC, Summary of product characteristics; SVR, Sustained virologic response; TN, Treatment naïve; wks, weeks.

Treatment duration

Table 106: GT1/1a/1b TE: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir/velpatasvir (12 wks)	99.7% (327/328)	12.0	0.3% (1/328)	2.0	0.0%	0.0	ASTRAL-1 (70); one GT1a NC patient discontinued at day 13, treatment history of this patient is not available
Ledipasvir/sofosbuvir (12 wks)	100.0% (109/109)	12.0	0.0%	0.0	0.0%	0.0	ION-2 (102)
Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)	100.0% (111/111)	12.0	0.0%	0.0	0.0%	0.0	PEARL-II (111)
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	98.2% (292+204)/(297+208)	12.0	1.4% (3+4)/(297+208)	6.0	0.4%	6.0	SAPPHIRE-II (126) for NC and TURQUOISE-II for CC‡ (137)
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	94.8% (172-9)/(172)	24.0	2.3% (4/172)	12.0	2.9%	12.0	TURQUOISE-II‡ (137)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	97.6% (285/292)	12.0	1.7% (285/292)	5.3	0.7%	4.8	Assumed equal to GT1 TN patients (NEUTRINO) (19)
Sofosbuvir + daclatasvir (12 wks) For Sofosbuvir + daclatasvir + RBV (24 wks) data assumed to be equivalent to sofosbuvir + daclatasvir (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	Assumed equal to GT1 TN patients reported by Sulkowski et al (AI444040 study group) (81)
Simeprevir + Peg-IFN2a + RBV (RGT)	93.3% (729/781)	48.0	6.7%	0.0	0.0%	12.0	According to 2015 EASL guidelines, SMV should be adminisered for 12 weeks with PR. PR should then be administered alone for an additional 12 wks for prior relapsers and for an additional 36 weeks in prior partial and null responders- Discontinuations to other reasons is from a pooling of

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
							QUEST1/2 (120, 121) + PROMISE (115)‡
Peg-IFN2a + RBV (48 wks)	37.9% (132-82)/132	48.0	6.1% (8/132)	19.5	56.1%	19.5	Telaprevir NICE STA 2011 (REALIZE - Table 30 - Table 31); Numbers of weeks for discontinuation due to AEs or other reasons calibrated to have an overall treatment duration equal to 30.2 (average between 30.0 and 30.4) (195)

AEs, Adverse events; Peg-IFN2a, Pegylated interferon alfa-2a; RBV, Ribavirin; TE, Treatment-experienced; wks, Weeks;
† Calculated as 100%-sum of the other categories
‡ Number of weeks for discontinuation is an assumption

Treatment-related adverse events

Table 107: GT1/1a/1b TE: Treatment safety

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir/velpatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ASTRAL-1 (70)
Ledipasvir/sofosbuvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ION-2 (102)
Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Assumption
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Assumption
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Assumption

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	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 (19)
Sofosbuvir + daclatasvir (12 wks) For Sofosbuvir + daclatasvir + RBV (24 wks) data assumed to be equivalent to sofosbuvir + daclatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Assumption
Simeprevir + Peg-IFN2a + RBV (RGT)	0.0%	0.0%	0.0%	0.1% (1/718)	0.3% (2/718)	1.0%	1.0%	0.0%	10.0%	0.0%	0.0%	Pooling QUEST1/2 (120, 121) + PROMISE (115)
Peg-IFN2a + RBV (48 wks)	1.0%	0.0%	0.0%	0.1%	0.1%	29.55% (10+29)/(30+102)	29.55% (10+29)/(30+102)	3.03% (0+1+3+0)/(30+102)	14.39% (2+1+13+3)/(30+102)	0.00%	0.00%	Anaemia/neutropenia/thrombocytopenia: Kaufman et al (2011) (REALIZE) (193); Other: FDA; 0% assumed for severe liver injury

AEs, Adverse events; GT, genotype; Peg-IFN2a, Pegylated interferon alfa-2a; RBV, Ribavirin; TE, Treatment-experienced; wks, Weeks;
‡ Number of weeks for discontinuation is an assumption

Treatment-specific quality of life

Table 108: GT1/1a/1b TE: Treatment-specific quality of life

Strategy	Utility increment/decrement	Source
Sofosbuvir/velpatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Ledipasvir/sofosbuvir (12 wks)	4.43%	ION trials (LDV/SOF 12 wks) (27, 101, 102)
Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)

Strategy	Utility increment/decrement	Source
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	-3.25%	Assumed equal to ION trials for LDV/SOF + RBV (12 wks)
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	-1.00%	Assumed equal to ION trials for LDV/SOF + RBV (24 wks)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	-14.52%	NEUTRINO (19)
Sofosbuvir + daclatasvir (12 wks) For Sofosbuvir + daclatasvir + RBV (24 wks) data assumed to be equivalent to sofosbuvir + daclatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Simeprevir + Peg-IFN2a + RBV (RGT)	-14.61%	Assumed equal to telaprevir (NICE TA252 (REALIZE trial))
Peg-IFN2a + RBV (48 wks)	-14.77%	Wright, 2006 (UK mild HCV trial) (165)

LDV, ledispavir; Peg-IFN2a, Pegylated interferon alfa-2a; RBV, Ribavirin; RGT, Response Guided Therapy; SOF, sofosbuvir; wks, Weeks

5.6.1.5 GT2 TN

SVR

Table 109: GT2 TN: SVR

Strategy	Initial state	SVR % (n/N)	Source
Sofosbuvir/velpatasvir (12 wks)	Non-cirrhotic	99.0% (99/100)	ASTRAL-2 (28)
	Cirrhotic	100.0% (15/15)	ASTRAL-2 (28)
Sofosbuvir + RBV (12 wks)	Non-cirrhotic	95.8% (92/96)	ASTRAL-2 (28)
	Cirrhotic	93.3% 14/15	ASTRAL-2 (28)
Peg-IFN2a + RBV (24 wks)	Non-cirrhotic	80.6%	Bucher indirect treatment comparison (See Section 4.10.9.1)
	Cirrhotic	71.5%	Bucher indirect treatment comparison (See Section 4.10.9.1)

GT, Genotype; CSR, Clinical Study Report; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; SmPC, Summary of product characteristics; wks, weeks

Treatment duration

Table 110: GT2 TN: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir/velpatasvir (12 wks)	99.3% (133/134)	12.0	0.7% (1/134)	1.0	0.0%	0.0	ASTRAL-2 (28)
Sofosbuvir + RBV (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	ASTRAL-2 (28)
Peg-IFN2a + RBV (24 wks)	82.1% (55/67)	24.0	11.9% (8/67)	14.9	6.0%	9.3	FISSION (19)

AE, Adverse event; CSR, Clinical study report; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TN, Treatment-naïve; wks, weeks
† Calculated as 100%-sum of the other categories

Treatment-related adverse events

Table 111: GT2 TN: Treatment safety

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir/velpatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ASTRAL-2 (28)
Sofosbuvir + RBV (12 wks)	0.4% (1/256)	0.0%	0.0%	0.0%	0.0%	0.6% ((1+1)/(256+84))	0.6% ((1+1)/(256+84))	0.0%	0.0%	0.0%	0.0%	VALENCE (149) and FISSION (19)
Peg-IFN2a + RBV (24 wks)	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 (19)

AE, Adverse event; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TN, Treatment-naïve; wks, weeks

Treatment-specific quality of life

Table 112: GT2 TN: Treatment-specific quality of life

Strategy	Utility increment/decrement	Source
Sofosbuvir/velpatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Sofosbuvir + RBV (12 wks)	-2.55%	FISSION (19)
Peg-IFN2a + RBV (24 wks)	-14.77%	Wright, 2006 (UK mild HCV trial) (165)

GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TN, Treatment-naïve; wks, weeks

5.6.1.6 GT2 TE

SVR

Table 113: GT2 TE: SVR

Strategy	Initial state	SVR % (n/N)	Source
Sofosbuvir/velpatasvir (12 wks)	Non-cirrhotic	100.0% (15/15)	ASTRAL-2 (28)
	Cirrhotic	100.0% (4/4)	ASTRAL-2 (28)
Sofosbuvir + RBV (12 wks)	Non-cirrhotic	81.3% (13/16)	ASTRAL-2 (28)
	Cirrhotic	100% (4/4)	ASTRAL-2 (28)
Peg-IFN2a + RBV (48 wks)	Non-cirrhotic	35.0% (0.625*0.53/0.375*0.05)	Lagging et al (151) And Shoeb et al (192)
	Cirrhotic	35.0% (0.625*0.53/0.375*0.05)	Lagging et al (151) And Shoeb et al (192)

GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; SmPC, Summary of product characteristics; TE, Treatment-experienced; wks, weeks

Treatment duration

Table 114: GT2 TE: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir/velpatasvir (12 wks)	99.3% (133/134)	12.0	0.7% (133/134)	1.0	0.0%	0.0	ASTRAL-2 (28)

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir + RBV (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	ASTRAL-2 (28)
Peg-IFN2a + RBV (48 wks)	63.2% (1-14/38)	48.0	36.8% (14/38)	24.0	0.0%	0.0	Lagging 2013 (151) (Average number of weeks of discontinuations due to AEs is an assumption)

AE, Adverse event; CSR, Clinical study report; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TE, Treatment-experienced
† Calculated as 100%-sum of the other categories

Treatment-related adverse events

Table 115: GT2 TE: Treatment safety

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir/velpatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ASTRAL-2 (28)
Sofosbuvir + RBV (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	1.6% (1+2)/(84+103)	1.6% (1+2)/(84+103)	0.0%	0.0%	0.0%	0.0%	VALENCE (149) and FUSION (31)
Peg-IFN2a + RBV (24 wks)	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 (19)

AE, Adverse event; GT, Genotype; NDA, No data available; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TN, Treatment-naïve; wks, weeks

Treatment-specific quality of life

Table 116: GT2 TE: Treatment-specific quality of life

Strategy	Utility increment/decrement	Source
Sofosbuvir/velpatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Sofosbuvir + RBV (12 wks)	-6.88%	FUSION (31)

Strategy	Utility increment/decrement	Source
Peg-IFN2a + RBV (24 wks)	-14.77%	Wright, 2006 (UK mild HCV trial) (165)

GT, Genotype; HCV, Hepatitis C virus; Peg-IFN2a, Peginterferon alfa-2a; Peg-IFN2b; RBV, Ribavirin; SMV, TE, Treatment-experienced; wks: weeks

5.6.1.7 GT4/5/6 TN

SVR

Table 117: GT4/5/6 TN: SVR

Strategy	Initial state	GT4		GT5		GT6	
		SVR % (n/N)	Source	SVR % (n/N)	Source	SVR % (n/N)	Source
Sofosbuvir/velpatasvir (12 wks)	Non-cirrhotic	100.0% (89/89)	ASTRAL-1 (70)	96.6% (28/29)	ASTRAL-1 (70)	100.0% (35/35)	ASTRAL-1 (70)
	Cirrhotic	100.0% (27/27)	ASTRAL-1 (70)	100.0% (5/5)	ASTRAL-1 (70)	100.0% (6/6)	ASTRAL-1 (70)
Ledipasvir/sofosbuvir (12 wks)	Non-cirrhotic	95.2% (20/21)	Abergel et al 2015 (155)	94.4% (17/18)	Abergel et al 2015 (155)	96.0% (24/25)	Gane et al 2015 (98) (GT6)
	Cirrhotic	100.0% (1/1)	Abergel et al 2015 (155)	100.0% (3/3)	Abergel et al 2015 (155)	96.0% (24/25)	Gane et al 2015 (98) (GT6)
Ombitasvir/paritaprevir /ritonavir + RBV (12 wks)	Non-cirrhotic	100.0% (42/42)	PEARL-I (110) (abstract only)		No data available		No data available
	Cirrhotic	100.0% (42/42)	PEARL-I (110) (abstract only)		No data available		No data available
Ombitasvir/paritaprevir /ritonavir + RBV (24 wks)	Non-cirrhotic		Data not available		No data available		No data available
	Cirrhotic		Data not available		No data available		No data available
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	Non-cirrhotic	100.0% (33/33)	NEUTRINO (19); mainly GT4	100.0% (33/33)	NEUTRINO (19); mainly GT4	100.0% (33/33)	NEUTRINO (19); mainly GT4
	Cirrhotic	50.0% (1/2)	NEUTRINO (19); (mainly GT4)	50.0% (1/2)	NEUTRINO (19); (mainly GT4)	50.0% (1/2)	NEUTRINO (19); (mainly GT4)
Simeprevir + Peg-IFN + RBV (RGT)	Non-cirrhotic	84.4% (27/32)	RESTORE (HPC3011) (Moreno 2015 (156))	NA	NA	NA	NA
	Cirrhotic	66.7% (2/3)	RESTORE (HPC3011) (Moreno 2015 (156))	NA	NA	NA	NA
Daclatasvir + Peg-IFN	Non-cirrhotic	81.2% (56/69)	COMMAND-4	NA	NA	NA	NA

Strategy	Initial state	GT4		GT5		GT6	
		SVR % (n/N)	Source	SVR % (n/N)	Source	SVR % (n/N)	Source
+ RBV			(AI444042) (Hezode, 2015 (90)), as presented in SmPC				
	Cirrhotic	77.8% (7/9)	COMMAND-4 (AI444042) (Hezode, 2015 (90)), as presented in SmPC	NA	NA	NA	NA
Peg-IFN2a + RBV (48 wks)	Non-cirrhotic	45.0% (17/38)	COMMAND-4 (AI444042) (Hezode, 2015 (90)), as presented in SmPC	45.0% (17/38)	Assumed equal to COMMAND-4 (AI444042) (Hezode, 2015 (90))	45.0% (17/38)	Assumed equal to COMMAND-4 (AI444042) (Hezode, 2015 (90))
	Cirrhotic	25.0% (1/4)	COMMAND-4 (AI444042) (Hezode, 2015 (90)), as presented in SmPC	25.0% (1/4)	Assumed equal to COMMAND-4 (AI444042) (Hezode, 2015 (90))	25.0% (1/4)	Assumed equal to COMMAND-4 (AI444042) (Hezode, 2015 (90))

EASL, European Association for the Study of Liver; GT, Genotype; HCV, Hepatitis C virus; Peg-IFN2a, Peginterferon alfa-2a; Peg-IFN2b, Peginterferon alfa-2b; RBV, Ribavirin; TE, Treatment experienced; TN, Treatment-naive; wks, weeks

Treatment duration

Table 118: GT4/5/6 TN: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	wk	% patients	wk	% patients†	wk	
Sofosbuvir/velpatasvir (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	ASTRAL-1 (70)
Ledipasvir/sofosbuvir (12 wks)	97.1% ((22+21+23)/(22+21+25))	12.0	0.0%	0.0	2.9%	6.0	Abergel et al 2015 (155) (GT4-5) and Gane et al 2015 (98) (GT6); Number of weeks for discontinuation due to other reasons is an assumption
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	PEARL-I (110) (abstract only)
Ombitasvir/paritaprevir/ritonavir + RBV (24							No data available

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	wk	% patients	wk	% patients†	wk	
wks)							
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	NEUTRINO (19)
Peg-IFN2a + RBV (48 wks)	62.0% (26/42)	48.0	7.0% (3/42)	24.0	31.0% (13/42)	24.0	COMMAND-4 (AI444042) (Hezode, 2015 (90))

AE, Adverse event; EASL, European Association for the Study of Liver; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; SOF, Sofosbuvir; TN, Treatment-naïve; wk, Weeks
† Calculated as 100%-sum of the other categories

Treatment-related adverse events

Table 119: GT4/5/6 TN: Treatment safety

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir/velpatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ASTRAL-1 (70)
Ledipasvir/sofosbuvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Abergel et al 2015 (155) (GT4-5) and Gane et al 2015 (98) (GT6)
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	PEARL-I (110)
Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)												No data available
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	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%	NEUTRINO (19)
Peg-IFN2a + RBV (48 wks)	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 (19)

AE, Adverse event; EASL, European Association for the Study of Liver; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TN, Treatment-naïve; wks, weeks

Treatment-specific quality of life

Table 120: GT4/5/6 TN: Treatment-specific quality of life

Strategy	Utility increment/decrement	Source
Sofosbuvir/velpatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Ledipasvir/sofosbuvir (12 wks)	4.43%	ION trials (LDV/SOF 12 wks) (27, 101, 102)
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	-3.25%	Assumed equal to ION trials for LDV/SOF + RBV (12 wks)
Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)	-1.00%	Assumed equal to ION trials for LDV/SOF + RBV (24 wks)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	-14.52%	NEUTRINO (19)
Peg-IFN2a + RBV (48 wks)	-14.77%	Wright, 2006 (UK mild HCV trial) (165)

HCV, Hepatitis C virus; LDV, ledipasvir; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; SOF, sofosbuvir; wks, weeks

5.6.1.8 GT4/5/6 TE

SVR

Table 121: GT4/5/6 TE: SVR

Strategy	Initial state	GT4		GT5		GT6	
		SVR % (n/N)	Source	SVR % (n/N)	Source	SVR % (n/N)	Source
Sofosbuvir/velpatasvir (12 wks)	Non-cirrhotic	100.0%	ASTRAL-1 (70)	100.0%	ASTRAL-1 (70)	100.0%	ASTRAL-1 (70)
	Cirrhotic	100.0%	ASTRAL-1 (70)	100.0%	ASTRAL-1 (70)	100.0%	ASTRAL-1 (70)
Ledipasvir/sofosbuvir (12 wks)	Non-cirrhotic	84.6% (11/13)	Abergel et al 2015 (155)	100.0% (14/14)	Abergel et al 2015 (155)	96.0% (24/25)	Gane et al 2015 (98)
	Cirrhotic	100.0% (9/9)	Abergel et al 2015 (155)	83.3% (5/6)	Abergel et al 2015 (155)	96.0% (24/25)	Gane et al 2015 (98)
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	Non-cirrhotic	100.0% (49/49)	PEARL-I (110)		No data available		No data available
	Cirrhotic	100.0% (49/49)	PEARL-I (110)		No data available		No data available
Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)	Non-cirrhotic		No data available		No data available		No data available
	Cirrhotic		No data available		No data available		No data available
Sofosbuvir + Peg-IFN2a + RBV (12	Non-cirrhotic	100.0% (33/33)	NEUTRINO (19); mainly GT4	100.0% (33/33)	NEUTRINO (19); mainly GT4	100.0% (33/33)	NEUTRINO (19); mainly GT4

Strategy	Initial state	GT4		GT5		GT6	
		SVR % (n/N)	Source	SVR % (n/N)	Source	SVR % (n/N)	Source
wks)	Cirrhotic	50.0% (1/2)	NEUTRINO (19); (mainly GT4)	50.0% (1/2)	NEUTRINO (19); (mainly GT4)	50.0% (1/2)	NEUTRINO (19); (mainly GT4)
Simeprevir + Peg-IFN + RBV (RGT)	Non-cirrhotic	63.6% (11+17/12+32)	RESTORE (HPC3011) (Moreno 2015 (156))	NA	NA	NA	NA
	Cirrhotic	46.4% (8+5/10+18)	RESTORE (HPC3011) (Moreno 2015 (156))	NA	NA	NA	NA
Daclatasvir + Peg-IFN + RBV (	Non-cirrhotic	81.2% (56/69)	No data available; conservatively assumed to be equivalent to TN patients in COMMAND-4 (AI444042) (Hezode, 2015 (90))	NA	NA	NA	NA
	Cirrhotic	77.8% (7/9)	No data available; conservatively assumed to be equivalent to TN patients in COMMAND-4 (AI444042) (Hezode, 2015 (90))	NA	NA	NA	NA
Peg-IFN2a + RBV (48 wks)	Non-cirrhotic	45.0% (17/38)	No data available; assumed same as Study AI444042		No data available		No data available
	Cirrhotic	25.0% (1/4)	No data available; assumed same as Study AI444042		No data available		No data available

EASL, European Association for the Study of Liver; GT, Genotype; HCV, Hepatitis C virus; Peg-IFN2a, Peginterferon alfa-2a; Peg-IFN2b, Peginterferon alfa-2b; RBV, Ribavirin; TE, Treatment experienced; TN, Treatment-naive; wks, weeks

Treatment duration

Table 122: GT4/5/6 TE: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	wk	% patients	wk	% patients†	wk	
Sofosbuvir/velpatasvir (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	ASTRAL-1 (70)
Ledipasvir/sofosbuvir (12 wks)	97.0%	12.0	0.0%	0.0	3.0%	6.0	Abergel et al 2015 (155) (GT4-5) and Gane et al

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	wk	% patients	wk	% patients†	wk	
	(22+20+23)/(22+20+25)						2015 (98) (GT6); Number of weeks for discontinuation are assumptions
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	PEARL-I (110)
Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)							No data available
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	NEUTRINO (19)
Peg-IFN2a + RBV (48 wks)	62.0% (26/42)	48.0	7.0% (3/42)	24.0	31.0% (13/42)	24.0	COMMAND-4 (AI444042) (Hezode, 2015 (90))

AE, Adverse event; EASL, European Association for the Study of Liver; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; SOF, Sofosbuvir; TN, Treatment-naïve; wk, Weeks

† Calculated as 100%-sum of the other categories

Treatment-related adverse events

Table 123: GT4/5/6 TE: Treatment safety

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir/velpatasvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ASTRAL-1 (70)
Ledipasvir/sofosbuvir (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Abergel et al 2015 (155) (GT4-5) and Gane et al 2015 (98) (GT6)
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	PEARL-I (110)
Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)												No data available
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	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 to equal to NEUTRINO (19)
Peg-IFN2a + RBV (48	0.4%	0.0%	0.0%	0.0%	0.0%	0.8%	0.8%	2.1%	3.3%	0.4%	0.0%	FISSION (19)

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
wks)	(1/243)					(2/243)	(2/243)	(5/243)	(8/243)	(1/243)		

AE, Adverse event; EASL, European Association for the Study of Liver; GT, Genotype; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; TE, Treatment-experienced; wks, weeks

Treatment-specific quality of life

Table 124: GT4/5/6 TE: Treatment-specific quality of life

Strategy	Utility increment/decrement	Source
Sofosbuvir/velpatasvir (12 wks)	4.43%	Assumed equal to ION trials for LDV/SOF (12 wks)
Ledipasvir/sofosbuvir (12 wks)	4.43%	ION trials (LDV/SOF 12 wks) (27, 101, 102)
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	-3.25%	Assumed equal to ION trials for LDV/SOF + RBV (12 wks)
Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)	-1.00%	Assumed equal to ION trials for LDV/SOF + RBV (24 wks)
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	-14.52%	NEUTRINO (19)
Peg-IFN2a + RBV (48 wks)	-14.77%	Wright, 2006 (UK mild HCV trial) (165)

LDV, ledipasvir; Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; SOF, sofosbuvir; wks, weeks;

5.6.1.9 Decompensated cirrhosis

Treatment naïve and treatment experience populations are identical in the DCC population

SVR

Table 125: Decompensated cirrhosis: SVR

Strategy	Initial state	SVR % (n/N)	Source
Sofosbuvir/velpatasvir + RBV (12 wks)	Decompensated cirrhotic	94.3% (82/87)	ASTRAL -4 (71)
Ledipasvir/sofosbuvir + RBV (12 wks)	Decompensated cirrhotic	86.4% (19/22)	SOLAR-1 (SmPC & Charlton 2015 (21, 128))

Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; SVR, Sustained virologic response; TE, Treatment experienced; TN, Treatment naïve; wks, Weeks

Treatment duration

Table 126: DDC: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients†	# weeks	
Sofosbuvir/velpatasvir + RBV (12 wks)	95.4% (87-4)/87	12.0	4.6% (4/87)	6.0	0.0%	0.0	ASTRAL-4 (71)
Ledipasvir/sofosbuvir + RBV (12 wks)	98.1% (30+21)/(30+22)	12.0	1.9% (0+1)/(30+22)	6.0	0.0%	0.0	Charlton et al 2015 (128); Numbers of weeks for discontinuations are assumptions

Peg-IFN2a, Peginterferon alfa-2a; RBV, Ribavirin; wks, weeks
† Calculated as 100%-sum of the other categories

Treatment-related adverse events

Table 127: DCC: Treatment safety

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood transfusion)	Thrombocytopenia	Neutropenia	Depression	Severe liver injury	Source
Sofosbuvir/velpatasvir + RBV	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	ASTRAL-4 (71)
Ledipasvir/sofosbuvir + RBV (12 wks)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Charlton et al 2015 (128) (No data on grade 3/4 adverse events)

AE, adverse event; DCC, Decompensated cirrhosis; RBV, Ribavirin; wks, weeks

Treatment-specific quality of life

Table 128: DCC: Treatment-specific quality of life

Strategy	Utility increment/decrement	Source
Sofosbuvir/velpatasvir + RBV (12 wks)	-3.25%	Assumed equal to ION trials for LDV/SOF + RBV (12 wks)
Ledipasvir/sofosbuvir + RBV (12 wks)	-3.25%	ION trials (LDV/SOF + RBV 12 wks) (27, 101, 102)

LDV, Ledipasvir; RBV, Ribavirin; SOF, Sofosbuvir; wks, weeks

5.6.2 *Assumptions*

As already mentioned, this model is similar to the model submitted to NICE for the recent appraisals of SOF (TA330) and LDV/SOF (TA363). Clinical data have been updated where required, and model parameters have been re-reviewed and updated. In particular, new data for the non-cirrhotic to cirrhotic TP has been incorporated (see Table 81) based on the results of a targeted literature review. This review was conducted in order to take into account ERG comments on the approach taken in the LDV/SOF submission, and to review relevant studies published until the present time, in order to identify the most appropriate source for this key model transition. In addition, improvements to the usability of the model in light of the LDV/SOF ERG comments have been made (196).

The SOF/VEL model assumptions are listed below. These are compared and discussed against the assumptions made in previous models:

- The Gilead clinical trial patients were randomised based on cirrhotic and non-cirrhotic status. Study results were reported for the entire cohort as well as non-cirrhotic and cirrhotic cohorts. Based on the study design protocol, no distinction was made between mild and moderate patients. Consequently, it was necessary to pool all patients with F0-F3 CHC together as non-cirrhotic patients
- A small risk of progression may exist among patients with moderate CHC achieving SVR (unlike for the mild stage, where SVR is considered equivalent to cure). In this respect, the models by Shepherd et al, 2007 (162) and Hartwell et al, 2011 (163) assumed patients who achieved an SVR from mild or moderate CHC to have the same risk of developing HCC as the general population. This is consistent with end of treatment biopsies from previously reported trials that did not find any evidence of disease progression following an SVR. Therefore a zero risk of progression for the non-cirrhotic CHC patients was used for the base-case analysis. Nevertheless, the model allowed the possibility of recurrence or re-infection in non-cirrhotic, compensated cirrhotic and decompensated cirrhotic patients that had reached SVR.
- Shepherd et al, 2007 (162) and Hartwell et al, 2011 (163) included as sensitivity analysis the possibility for mild CHC patients to spontaneously reach SVR. This was not taken into account in our model since this specific health state was not included in our model
- Different health states representing decompensated cirrhosis (such as ascites, hepatic encephalopathy and hepatorenal syndrome) were collapsed into one (i.e., like in Shepherd et al, 2007 (162) and Hartwell et al, 2011 (163) but unlike in Bennett et al, 1997 (184)). The advantage of collapsing those states into one is that this allows for a patient to have several complications simultaneously, which often happens in reality. Assigning costs to individual complications and using the average could lead to biased results if complications have substantially different costs and durations. The problem is the same with utilities for calculating quality-adjusted life years. For example, if complications with high costs are generally associated with short durations, the model would overestimate the cost of decompensated cirrhosis. In any case, it may be argued that it is not feasible to

estimate costs for different types of complications separately since in reality many patients live with several complications simultaneously, and there are interactions between those complications on costs. Also, the recommended approach is to use observational data on a representative sample of patients with decompensated cirrhosis (who may suffer different complications or combinations of complications). This approach has been adopted by Wright et al, 2006 (165) in particular.

- DCC patients with or without SVR were assumed to be candidates for liver transplantation
- During treatment, patients were assumed to experience a decrement in HRQL resulting from treatment adverse events
- Patients do not die of non-CHC causes during the treatment period. This is the same assumption made in the LDV/SOF NICE submission (TA363). The ERG recognised that the magnitude of the bias introduced by this assumption is likely to be small and will favour treatment options given over a longer mean duration.
- Background mortality is assumed to be the same as for the general population
- While patients with compensated cirrhosis that reach SVR are followed-up over a lifetime (and therefore follow-up costs are applied during that time period), non-cirrhotic patients with SVR are only followed until the end of year two
- No patients move from the HCC health state to the LT health state. Patient movement between these health states is tested in the sensitivity analysis based on opinions from external KOLs
- It was assumed that achieving SVR is permanent and that transitioning back to non-SVR health states is not possible. This assumption was validated by external KOLs and is consistent with other CHC economic models (57, 162, 163, 165).
- The model assumes that no quality of life, or adverse event and cost implications persist once treatment is discontinued. Patients return to the quality of life utility value relevant to the post treatment health state they are in, and future adverse events and their associated costs cannot occur.

5.7 *Base-case results*

- **The company evidence submission for SOF/VEL made to NICE on the deadline on Friday 20th May 2016 used the proposed confidential fixed price of SOF/VEL, and anticipated list prices of comparators, for all analyses. This approach was aligned with discussion at the Decision Problem meeting for this appraisal on 24th March 2016. Following request from NICE on Thursday 26th May, revised analyses have been prepared, in which:**
  - **the proposed confidential fixed price of SOF/VEL is used for all analyses that do not contain either ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) or daclatasvir**
  - **the anticipated UK anticipated list price of SOF/VEL is used for all analyses containing either ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) or daclatasvir**
- **It was acknowledged by NICE on Thursday 26th May that "the anticipated**

list price versus anticipated list price analyses would also be non-informative to some extent". Gilead agrees that the analyses using the anticipated UK anticipated list price of SOF/VEL will not be informative and that analyses which use the proposed confidential fixed price of SOF/VEL should be the primary analyses considered for appraisal and decision making purposes.

- **It is also clear that for some of the analyses in which the anticipated UK anticipated list price of SOF/VEL is used, differences in total costs and/or QALYs versus some comparators are extremely small. This renders the corresponding incremental cost-effectiveness ratios extremely sensitive to very small changes in costs and QALYs, which further undermines the usefulness of these results for appraisal and decision making purposes.**
- **Nevertheless, following the request from NICE for these revised analyses (which is considered to be outside of the usual STA process) these have been provided. The title of each results table indicates whether the proposed confidential fixed price of SOF/VEL or the anticipated UK anticipated list price of SOF/VEL has been used in the analysis.**

5.7.1 *Summary of base-case results*

Base-case incremental analysis results for all patient populations are presented stratified by genotype, treatment-experience and cirrhotic status in Sections 5.7.2.1 through 5.7.2.11.

Results are summarised below for each genotype.

GT3 (list price for SOF/VEL IFN ineligible patients only)

- ***For GT3 treatment naïve patients without cirrhosis*** SOF/VEL is highly cost-effective with an ICER of £15,199 versus Peg-IFN+RBV 24 weeks, with "no treatment" being dominated by Peg-IFN+RBV. In this patient group SOF/VEL provides the first DAA-based regimen that can be used for all patients with GT3 infection who are treatment-naïve without cirrhosis. SOF/VEL provides a highly effective and cost-effective treatment for a group for whom there is substantial unmet clinical need.
- ***For GT3 treatment naïve patients without cirrhosis who are IFN-ineligible***, SOF+DCV 12 weeks is the only DAA-based NICE-recommended regimen available, to which access is further restricted to patients who are F3/F4. In this group SOF/VEL 12 weeks dominates SOF+DCV and has an ICER of £5,287 versus no treatment.
- For all other ***GT3 populations***, including ***treatment-naïve cirrhotic, treatment-experienced non-cirrhotic and treatment-experienced cirrhotic***, SOF/VEL 12 weeks is cost-effective versus no treatment and Peg-IFN+RBV 24/48 weeks with ICERs <£5,000. SOF+Peg-IFN+RBV 12 weeks is either dominated by SOF/VEL or has an ICER >£100,000.
- For all other ***GT3 IFN-ineligible populations***, including ***treatment-naïve cirrhotic, treatment-experienced non-cirrhotic and treatment-experienced***

cirrhotic, SOF/VEL 12 weeks is cost-effective versus no treatment and all active comparators with ICERs <£10,000.

GT1 (anticipated list price of SOF/VEL)

- In ***GT1 treatment-naïve non-cirrhotic*** patients the ICER for SOF/VEL 12 weeks versus no treatment was £7,028 per QALY. The ICER for SOF/VEL compared to LDV/SOF 8 weeks was £73,604.
- For all other ***GT1 populations***, including ***treatment-naïve cirrhotic, treatment-experienced non-cirrhotic and treatment-experienced cirrhotic,*** SOF/VEL 12 weeks is cost-effective versus no treatment with ICERs <£10,000. All other regimens are either dominated or dominated by the principle of extended dominance, with the exception of SOF+DCV 12w where the ICER vs SOF/VEL is £398,971.
- For ***sub-genotype analyses in 1a,*** the Abbvie regimens (OBV/PTV/RTV+DSV±RBV 12/24 weeks) were always dominated by SOF/VEL 12 weeks, except in GT1a treatment-experienced non-cirrhotic patients where SOF/VEL has an ICER of £41,741 vs OBV/PTV/RTV+DSV+RBV 12 weeks
- For ***sub-genotype analyses in 1b,*** the Abbvie regimens (OBV/PTV/RTV+DSV±RBV 12 weeks) dominated SOF/VEL.

GT2 (discounted price of SOF/VEL)

- In ***GT2 treatment-naïve non-cirrhotic*** patients SOF/VEL has an ICER of £32,595 versus Peg-IFN+RBV 24 weeks. This ICER is discussed further in Section 5.7.1.1.
- In ***GT2 treatment-naïve cirrhotic*** patients SOF/VEL has an ICER of ~£12,000 versus Peg-IFN+RBV 24 weeks, with no treatment being dominated.
- For ***GT2 treatment-experienced non-cirrhotic and treatment-experienced cirrhotic,*** patients SOF/VEL 12 weeks is cost-effective versus no treatment and Peg-IFN+RBV 48 weeks with ICERs <£7,000. SOF+RBV 12 weeks is either dominated (non-cirrhotic) or has an ICER >£1.7 million (cirrhotic) versus SOF/VEL 12 weeks.
- In analyses of ***GT2 IFN-ineligible*** patients, which include SOF+RBV 12 weeks as an option for treatment-naïve patients, this regimen is dominated by SOF/VEL in both non-cirrhotic and cirrhotic cohorts.

GT4 (anticipated list price of SOF/VEL for non-cirrhotic patients only)

- In **GT4 non-cirrhotic treatment-naïve and -experienced** patients, the ICER for SOF/VEL was £380,526 per QALY vs ombitasvir/paritaprevir/ritonavir + RBV. In **GT4 cirrhotic treatment-naïve and -experienced** patients SOF/VEL is highly cost-effective with it either dominating other options or having ICERs <£7,000

GT 5/6 (discounted price of SOF/VEL)

- Across all analyses of GT5 and GT6 patients stratified by treatment experience and cirrhotic status, SOF/VEL is highly cost-effective with it either dominating other options or having ICERs <£7,000.

Decompensated cirrhosis (discounted price of SOF/VEL)

- For decompensated patients, the current treatment option available is LDV/SOF+RBV for 12 weeks. In both treatment-naïve and treatment-experienced patients SOF/VEL+RBV 12 weeks is both cheaper and more efficacious, meaning that it dominates this current standard of care.

5.7.1.1 Discussion of GT2 treatment-naïve non-cirrhotic

- While the ICER for SOF/VEL 12 weeks versus Peg-IFN+RBV 24 weeks is slightly in excess of £30,000/QALY gained, an important feature of patients with CHC GT2 should also be taken into consideration when drawing conclusions on the likely cost-effectiveness of SOF/VEL 12 weeks in this patient population.
- In line with CHC treatment guidelines (Section 3.6) and previous NICE technology appraisals (Section 3.5), it is clear that the ability to reliably determine HCV genotype remains fundamental in making appropriate prescribing choices. In the UK NHS setting, the assay platform that is routinely used to determine genotype is the VERSANT HCV Genotype 2.0 Assay Line Probe Assay (LiPA, Siemens, Germany). This assay uses sequence information from the 5' and core regions of the viral genome.
- However, in patients who have been exposed to multiple HCV strains it is possible for the virus (through recombination) to contain genetic material from more than one genotype. This is often referred to as a chimeric form. Data from the literature suggests that this may be of particular clinical relevance in CHC genotype 2. For example, a recent publication has noted a recombinant strain in samples from patients who acquired HCV infection in Russia and countries of the Caucasus region, in which a combination genotype of 2k and genotype 1b was observed (197). Importantly, this determination can only be made when the full length of the virus gene is sequenced using next-generation sequencing techniques; this means that the assay routinely used in the UK NHS would tend to misclassify such an infection as a genotype 2 variant. The clinical relevance of this observation is reflected by the treatment that was prescribed for this patient. Initially treated with SOF+RBV 12 weeks based on the presumption of GT2 infection, the patient relapsed on completion of therapy. Next generation sequencing of the whole genome subsequently confirmed the presence of a 2k/1b recombinant strain. If the presence of 1b genotype had initially been known and used to determine treatment choice, SOF+RBV for 12 weeks would not have been prescribed, as this regimen is not licensed for HCV GT1b infection.
- In the UK NHS setting, misclassification of genotype may lead to suboptimal therapy, particularly in GT2 treatment-naïve patients without cirrhosis, for whom the only currently available treatment is Peg-IFN+RBV 24 weeks. These recombinant GT2 forms are more likely to be present in migrants from the countries of former Soviet states and the Caucasus region (198). Although the genetic epidemiology of such recombinant forms is yet to be fully characterised, it is likely that they are underdiagnosed by current techniques. In this way, not only are clinical outcomes likely to be suboptimal, transmission of the hepatitis C virus is also likely to be potentiated amongst this patient group.

- In the specific context of genotype misclassification the highly efficacious nature of SOF/VEL across all CHC genotypes is of particular value in GT2 infection. As such, patient access to SOF/VEL, without restrictions by CHC genotype or eligibility for IFN treatment represents the optimal approach to improving clinical outcomes in CHC GT2 while also enabling a meaningful impact on the societal burden of CHC in the UK.

5.7.2 *Base-case incremental cost effectiveness analysis results*

5.7.2.1 GT3 overall

GT3 treatment-naïve non-cirrhotic

Table 129: Base-case results: GT3 treatment-naïve non-cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Peg-IFN + RBV (24 wks)	[redacted]	20.85	[redacted]					
No treatment	[redacted]	18.12	[redacted]	£6,368	-2.73	-3.16	Dominated	Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	21.84	[redacted]	£18,958	0.99	1.25	£15,199	£15,199

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT3 treatment-naïve cirrhotic

Table 130: Base-case results: GT3 treatment-naïve cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.36	[redacted]					
Peg-IFN + RBV (24 wks)	[redacted]	11.94	[redacted]	£1,408	2.59	1.61	£876	£876
Sofosbuvir/velpatasvir (12 wks)	[redacted]	16.89	[redacted]	£14,020	7.54	4.85	£2,892	£3,893
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	16.76	[redacted]	£23,937	7.40	4.73	£5,058	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT3 treatment-experienced non-cirrhotic

Table 131: Base-case results: GT3 treatment-experienced non-cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	17.45	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	18.70	[redacted]	£3,588	1.25	1.39	£2,575	£2,575
Sofosbuvir/velpatasvir (12 wks)	[redacted]	20.36	[redacted]	£14,144	2.91	3.60	£3,926	£4,779
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	20.46	[redacted]	£22,878	3.01	3.69	£6,206	£104,232

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT3 treatment-experienced cirrhotic

Table 132: Base-case results: GT3 treatment-experienced cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.27	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	12.26	[redacted]	£3,750	3.00	1.83	£2,050	£2,050
Sofosbuvir/velpatasvir (12 wks)	[redacted]	15.96	[redacted]	£13,516	6.69	4.33	£3,120	£3,904
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	15.70	[redacted]	£23,373	6.44	4.14	£5,647	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.2.2 GT3 IFN-ineligible

GT3 treatment-naïve non-cirrhotic IFN-ineligible

Table 133: Base-case results: GT3 treatment-naïve non-cirrhotic IFN-ineligible (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£18,686	18.12	12.83					
Sofosbuvir/velpatasvir (12 wks)	£42,010	21.84	17.24	£23,324	3.72	4.41	£5,287	£5,287
Sofosbuvir + daclatasvir (12 wks)	£66,141	21.08	16.34	£47,454	2.95	3.50	£13,544	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT3 treatment-naïve cirrhotic IFN-ineligible

Table 134: Base-case results: GT3 treatment-naïve cirrhotic IFN-ineligible (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
Sofosbuvir/velpatasvir (12 wks)	£60,544	16.89	9.82	£24,754	7.54	4.85	£5,107	£5,107
Sofosbuvir + daclatasvir + RBV (24 wks)	£88,194	14.08	8.00	£52,404	4.72	3.03	£17,315	Dominated
Sofosbuvir + RBV (24 wks)	£97,229	15.42	8.85	£61,438	6.06	3.87	£15,875	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT3 treatment-experienced non-cirrhotic IFN-ineligible

Table 135: Base-case results: GT3 treatment-experienced non-cirrhotic IFN-ineligible (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£17,647	17.45	12.37					
Sofosbuvir/velpatasvir (12 wks)	£42,525	20.36	15.98	£24,878	2.91	3.60	£6,906	£6,906
Sofosbuvir + daclatasvir (12 wks)	£66,538	19.74	15.20	£48,891	2.29	2.83	£17,272	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT3 treatment-experienced cirrhotic IFN-ineligible

Table 136: Base-case results: GT3 treatment-experienced cirrhotic IFN-ineligible (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,361	9.27	4.93					
Sofosbuvir/velpatasvir (12 wks)	£59,612	15.96	9.26	£24,251	6.69	4.33	£5,599	£5,599
Sofosbuvir + daclatasvir + RBV (24 wks)	£84,651	14.48	8.29	£49,290	5.21	3.37	£14,640	Dominated
Sofosbuvir + RBV (24 wks)	£98,396	13.76	7.79	£63,035	4.49	2.87	£21,999	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.2.3 GT1a overall

GT1a treatment-naïve non-cirrhotic

Table 137: Base-case results: GT1a treatment-naïve non-cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£16,304	18.97	13.63					
PegIFN + RBV (48 wks)	£20,880	20.35	15.22	£4,576	1.38	1.59	£2,883	£2,883
Ledipasvir/sofosbuvir (8 wks)	£29,713	21.73	17.10	£13,409	2.76	3.47	£3,868	£4,700
Simeprevir + PegIFN + RBV (RGT)	£33,817	21.40	16.61	£17,512	2.43	2.97	£5,890	Dominated
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	£39,101	21.82	17.20	£22,797	2.85	3.57	£6,392	Ext. Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£41,331	21.67	16.98	£25,027	2.69	3.35	£7,471	Dominated
Sofosbuvir/velpatasvir (12 wks)	£41,964	21.84	17.23	£25,660	2.86	3.60	£7,129	£92,436
Sofosbuvir + daclatasvir (12 wks)	£62,383	21.91	17.32	£46,079	2.94	3.69	£12,486	£224,726

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1a treatment-naïve cirrhotic

Table 138: Base-case results: GT1a treatment-naïve cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
PegIFN + RBV (48 wks)	£43,577	11.68	6.36	£7,787	2.33	1.39	£5,616	Ext. Dominated
Simeprevir + PegIFN + RBV (RGT)	£55,825	14.40	8.16	£20,035	5.04	3.18	£6,299	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	£59,242	17.45	10.18	£23,452	8.10	5.21	£4,504	£4,504
Ledipasvir/sofosbuvir (12 wks)	£60,349	16.98	9.88	£24,559	7.63	4.90	£5,009	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£61,014	15.91	9.16	£25,224	6.56	4.19	£6,021	Dominated
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	£92,126	16.96	9.84	£56,336	7.61	4.87	£11,572	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1a treatment-experienced non-cirrhotic

Table 139: Base-case results: GT1a treatment-experienced non-cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£15,332	18.18	13.08					
PegIFN + RBV (48 wks)	£21,412	18.72	13.66	£6,080	0.54	0.58	£10,451	Ext. Dominated
Simeprevir + PegIFN + RBV (RGT)	£38,537	20.21	15.59	£23,205	2.03	2.51	£9,248	Ext. Dominated
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	£38,610	20.54	16.18	£23,278	2.36	3.10	£7,520	£7,520
Sofosbuvir/velpatasvir (12 wks)	£41,303	20.58	16.24	£25,971	2.40	3.16	£8,218	£41,741
Ledipasvir/sofosbuvir (12 wks)	£41,891	20.53	16.17	£26,559	2.35	3.09	£8,588	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£43,169	20.01	15.45	£27,836	1.83	2.37	£11,743	Dominated
Sofosbuvir + daclatasvir (12 wks)	£61,747	20.64	16.32	£46,414	2.46	3.24	£14,326	£256,566

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1a treatment-experienced cirrhotic

Table 140: Base-case results: GT1a treatment-experienced cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,361	9.27	4.93					
PegIFN + RBV (48 wks)	£42,400	10.36	5.55	£7,039	1.10	0.62	£11,327	Ext. Dominated
Simeprevir + PegIFN + RBV (RGT)	£57,519	15.14	8.60	£22,158	5.87	3.68	£6,027	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	£57,610	16.76	9.78	£22,249	7.49	4.85	£4,587	£4,587
Ledipasvir/sofosbuvir (12 wks)	£60,288	15.75	9.12	£24,927	6.48	4.20	£5,941	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£60,643	14.83	8.50	£25,281	5.57	3.58	£7,068	Dominated
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	£90,077	16.50	9.58	£54,716	7.23	4.66	£11,751	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.2.4 GT1b overall

GT1b treatment-naïve non-cirrhotic

Table 141: Base-case results: GT1b treatment-naïve non-cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£16,304	18.97	13.63					
PegIFN + RBV (48 wks)	£20,880	20.35	15.22	£4,576	1.38	1.59	£2,883	£2,883
Ledipasvir/sofosbuvir (8 wks)	£29,713	21.73	17.10	£13,409	2.76	3.47	£3,868	£4,700
Simeprevir + PegIFN + RBV (RGT)	£33,817	21.40	16.61	£17,512	2.43	2.97	£5,890	Dominated
Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)	£37,508	21.88	17.29	£21,204	2.91	3.66	£5,801	£41,376
Sofosbuvir + PegIFN + RBV (12 wks)	£41,331	21.67	16.98	£25,027	2.69	3.35	£7,471	Dominated
Sofosbuvir/velpatasvir (12 wks)	£41,581	21.91	17.32	£25,276	2.94	3.69	£6,849	£116,355
Sofosbuvir + daclatasvir (12 wks)	£62,383	21.91	17.32	£46,079	2.94	3.69	£12,486	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1b treatment-naïve cirrhotic

Table 142: Base-case results: GT1b treatment-naïve cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
PegIFN + RBV (48 wks)	£43,577	11.68	6.36	£7,787	2.33	1.39	£5,616	Ext. Dominated
Simeprevir + PegIFN + RBV (RGT)	£55,825	14.40	8.16	£20,035	5.04	3.18	£6,299	Ext. Dominated
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	£56,300	17.45	10.17	£20,509	8.10	5.20	£3,947	£3,947
Sofosbuvir/velpatasvir (12 wks)	£59,959	17.12	9.97	£24,169	7.76	4.99	£4,842	Dominated
Ledipasvir/sofosbuvir (12 wks)	£60,349	16.98	9.88	£24,559	7.63	4.90	£5,009	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£61,014	15.91	9.16	£25,224	6.56	4.19	£6,021	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1b treatment-experienced non-cirrhotic

Table 143: Base-case results: GT1b treatment-experienced non-cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£15,332	18.18	13.08					
PegIFN + RBV (48 wks)	£21,412	18.72	13.66	£6,080	0.54	0.58	£10,451	Ext. Dominated
Ombitasvir/paritaprevir/ritonavir + dasabuvir (12 wks)	£37,246	20.64	16.32	£21,914	2.46	3.24	£6,764	£6,764
Simeprevir + PegIFN + RBV (RGT)	£38,537	20.21	15.59	£23,205	2.03	2.51	£9,248	Dominated
Sofosbuvir/velpatasvir (12 wks)	£40,944	20.64	16.32	£25,612	2.46	3.24	£7,905	Dominated
Ledipasvir/sofosbuvir (12 wks)	£41,891	20.53	16.17	£26,559	2.35	3.09	£8,588	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£43,169	20.01	15.45	£27,836	1.83	2.37	£11,743	Dominated
Sofosbuvir + daclatasvir (12 wks)	£61,747	20.64	16.32	£46,414	2.46	3.24	£14,326	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1b treatment-experienced cirrhotic

Table 144: Base-case results: GT1b treatment-experienced cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,361	9.27	4.93					
PegIFN + RBV (48 wks)	£42,400	10.36	5.55	£7,039	1.10	0.62	£11,327	Ext. Dominated
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	£55,073	16.60	9.66	£19,712	7.33	4.74	£4,163	£4,163
Simeprevir + PegIFN + RBV (RGT)	£57,519	15.14	8.60	£22,158	5.87	3.68	£6,027	Dominated
Sofosbuvir/velpatasvir (12 wks)	£58,342	16.45	9.58	£22,981	7.19	4.65	£4,942	Dominated
Ledipasvir/sofosbuvir (12 wks)	£60,288	15.75	9.12	£24,927	6.48	4.20	£5,941	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£60,643	14.83	8.50	£25,281	5.57	3.58	£7,068	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.2.5 GT1 overall

GT1 treatment-naïve non-cirrhotic

Table 145: Base-case results: GT1 treatment-naïve non-cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£16,304	18.97	13.63					
PegIFN + RBV (48 wks)	£20,880	20.35	15.22	£4,576	1.38	1.59	£2,883	£2,883
Ledipasvir/sofosbuvir (8 wks)	£29,713	21.73	17.10	£13,409	2.76	3.47	£3,868	£4,700
Simeprevir + PegIFN + RBV (RGT)	£33,817	21.40	16.61	£17,512	2.43	2.97	£5,890	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£41,331	21.67	16.98	£25,027	2.69	3.35	£7,471	Dominated
Sofosbuvir/velpatasvir (12 wks)	£41,829	21.86	17.27	£25,525	2.89	3.63	£7,028	£73,604
Sofosbuvir + daclatasvir (12 wks)	£62,383	21.91	17.32	£46,079	2.94	3.69	£12,486	£349,606

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1 treatment-naïve cirrhotic

Table 146: Base-case results: GT1 treatment-naïve cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
PegIFN + RBV (48 wks)	£43,577	11.68	6.36	£7,787	2.33	1.39	£5,616	Ext. Dominated
Simeprevir + PegIFN + RBV (RGT)	£55,825	14.40	8.16	£20,035	5.04	3.18	£6,299	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	£59,495	17.34	10.11	£23,705	7.98	5.13	£4,620	£4,620
Ledipasvir/sofosbuvir (12 wks)	£60,349	16.98	9.88	£24,559	7.63	4.90	£5,009	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£61,014	15.91	9.16	£25,224	6.56	4.19	£6,021	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1 treatment-experienced non-cirrhotic

Table 147: Base-case results: GT1 treatment-experienced non-cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£15,332	18.18	13.08					
PegIFN + RBV (48 wks)	£21,412	18.72	13.66	£6,080	0.54	0.58	£10,451	Ext. Dominated
Simeprevir + PegIFN + RBV (RGT)	£38,537	20.21	15.59	£23,205	2.03	2.51	£9,248	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	£41,176	20.60	16.27	£25,844	2.42	3.19	£8,106	£8,106
Ledipasvir/sofosbuvir (12 wks)	£41,891	20.53	16.17	£26,559	2.35	3.09	£8,588	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£43,169	20.01	15.45	£27,836	1.83	2.37	£11,743	Dominated
Sofosbuvir + daclatasvir (12 wks)	£61,747	20.64	16.32	£46,414	2.46	3.24	£14,326	£398,971

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1 treatment-experienced cirrhotic

Table 148: Base-case results: GT1 treatment-experienced cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,361	9.27	4.93					
PegIFN + RBV (48 wks)	£42,400	10.36	5.55	£7,039	1.10	0.62	£11,327	Ext. Dominated
Simeprevir + PegIFN + RBV (RGT)	£57,519	15.14	8.60	£22,158	5.87	3.68	£6,027	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	£57,869	16.65	9.71	£22,507	7.39	4.78	£4,709	£4,709
Ledipasvir/sofosbuvir (12 wks)	£60,288	15.75	9.12	£24,927	6.48	4.20	£5,941	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£60,643	14.83	8.50	£25,281	5.57	3.58	£7,068	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.2.6 GT2 overall

GT2 treatment-naïve non-cirrhotic

Table 149: Base-case results: GT2 treatment-naïve non-cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Peg-IFN + RBV (24 wks)	[redacted]	21.47	[redacted]					
No treatment	[redacted]	19.53	[redacted]	£4,519	-1.93	-2.49	Dominated	Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	21.89	[redacted]	£20,729	0.42	0.64	£32,595	£32,595

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT2 treatment-naïve cirrhotic

Table 150: Base-case results: GT2 treatment-naïve cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Peg-IFN + RBV (24 wks)	[redacted]	15.28	[redacted]					
No treatment	[redacted]	9.36	[redacted]	£5,475	-5.92	-3.75	Dominated	Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	17.45	[redacted]	£18,094	2.18	1.46	£12,384	£12,384

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT2 treatment-experienced non-cirrhotic

Table 151: Base-case results: GT2 treatment-experienced non-cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	18.66	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	19.44	[redacted]	£5,015	0.79	0.95	£5,285	£5,285
Sofosbuvir/velpatasvir (12 wks)	[redacted]	20.63	[redacted]	£16,394	1.97	2.76	£5,929	£6,266
Sofosbuvir + RBV (12 wks)	[redacted]	20.27	[redacted]	£26,989	1.62	2.24	£12,048	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT2 treatment-experienced cirrhotic

Table 152: Base-case results: GT2 treatment-experienced cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.27	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	12.26	[redacted]	£3,750	3.00	1.830	£2,050	£2,050
Sofosbuvir/velpatasvir (12 wks)	[redacted]	16.73	[redacted]	£11,490	7.46	4.830	£2,379	£2,580
Sofosbuvir + RBV (12 wks)	[redacted]	16.76	[redacted]	£19,644	7.49	4.834	£4,063	£1,774,630

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.2.7 GT2 IFN-ineligible

GT2 treatment-naïve non-cirrhotic IFN-ineligible

Table 153: Base-case results: GT2 treatment-naïve non-cirrhotic IFN-ineligible (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	19.53	[redacted]					
Sofosbuvir/velpatasvir (12 wks)	[redacted]	21.89	[redacted]	£16,210	2.35	3.13	£5,183	£5,183
Sofosbuvir + RBV (12 wks)	[redacted]	21.81	[redacted]	£24,875	2.28	3.02	£8,249	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT2 treatment-naïve cirrhotic IFN-ineligible

Table 154: Base-case results: GT2 treatment-naïve cirrhotic IFN-ineligible (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.36	[redacted]					
Sofosbuvir/velpatasvir (12 wks)	[redacted]	17.45	[redacted]	£12,619	8.10	5.21	£2,424	£2,424
Sofosbuvir + RBV (12 wks)	[redacted]	16.92	[redacted]	£21,994	7.56	4.85	£4,532	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT2 treatment-experienced non-cirrhotic IFN-ineligible

Table 155: Base-case results: GT2 treatment-experienced non-cirrhotic IFN-ineligible (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	18.66	[redacted]					
Sofosbuvir/velpatasvir (12 wks)	[redacted]	20.63	[redacted]	£16,394	1.97	2.76	£5,929	£5,929
Sofosbuvir + RBV (12 wks)	[redacted]	20.27	[redacted]	£26,989	1.62	2.24	£12,048	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT2 treatment-experienced cirrhotic IFN-ineligible

Table 156: Base-case results: GT2 treatment-experienced cirrhotic IFN-ineligible (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.27	[redacted]					
Sofosbuvir/velpatasvir (12 wks)	[redacted]	16.73	[redacted]	£11,490	7.46	4.83	£2,379	£2,379
Sofosbuvir + RBV (12 wks)	[redacted]	16.76	[redacted]	£19,644	7.49	4.83	£4,063	£1,774,630

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.2.8 GT4 overall

GT4 treatment-naïve non-cirrhotic

Table 157: Base-case results: GT4 treatment-naïve non-cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£15,956	19.09	13.75					
PegIFN + RBV (48 wks)	£20,510	20.45	15.32	£4,553	1.35	1.57	£2,895	£2,895
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	£36,192	21.91	17.31	£20,236	2.82	3.56	£5,682	£7,887
Sofosbuvir/velpatasvir (12 wks)	£41,682	21.91	17.32	£25,726	2.82	3.58	£7,194	£380,526

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT4 treatment-naïve cirrhotic

Table 158: Base-case results: GT4 treatment-naïve cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.36	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	11.79	[redacted]	£7,552	2.43	1.45	£5,191	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	17.45	[redacted]	£12,819	8.10	5.21	£2,462	£2,462
Ledipasvir/sofosbuvir (12 wks)	[redacted]	17.45	[redacted]	£23,146	8.10	5.21	£4,446	Dominated
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	13.45	[redacted]	£31,043	4.09	2.60	£11,920	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT4 treatment-experienced non-cirrhotic

Table 159: Base-case results: GT4 treatment-experienced non-cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£14,998	18.28	13.18					
PegIFN + RBV (48 wks)	£19,342	19.43	14.56	£4,344	1.15	1.38	£3,152	£3,152
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	£35,556	20.64	16.31	£20,558	2.35	3.13	£6,578	£9,282
Sofosbuvir/velpatasvir (12 wks)	£41,046	20.64	16.32	£26,048	2.35	3.14	£8,297	£380,526
Ledipasvir/sofosbuvir (12 wks)	£42,803	20.28	15.84	£27,806	2.00	2.66	£10,447	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT4 treatment-experienced cirrhotic

Table 160: Base-case results: GT4 treatment-experienced cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.27	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	11.54	[redacted]	£6,616	2.28	1.36	£4,849	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	16.76	[redacted]	£11,617	7.49	4.85	£2,395	£2,395
Ledipasvir/sofosbuvir (12 wks)	[redacted]	16.76	[redacted]	£21,934	7.49	4.85	£4,523	Dominated
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	13.06	[redacted]	£30,025	3.79	2.43	£12,376	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.2.9 GT5 overall

GT5 treatment-naïve non-cirrhotic

Table 161: Base-case results: GT5 treatment-naïve non-cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	19.09	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	20.45	[redacted]	£4,553	1.35	1.57	£2,895	£2,895
Sofosbuvir/velpatasvir (12 wks)	[redacted]	21.81	[redacted]	£15,512	2.72	3.45	£4,491	£5,827

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT5 treatment-naïve cirrhotic

Table 162: Base-case results: GT5 treatment-naïve cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.36	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	11.79	[redacted]	£7,552	2.43	1.45	£5,191	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	17.45	[redacted]	£12,819	8.10	5.21	£2,462	£2,462
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	13.45	[redacted]	£31,043	4.09	2.60	£11,920	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT5 treatment-experienced non-cirrhotic

Table 163: Base-case results: GT5 treatment-experienced non-cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	18.28	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	19.43	[redacted]	£4,344	1.15	1.38	£3,152	£3,152
Sofosbuvir/velpatasvir (12 wks)	[redacted]	20.64	[redacted]	£15,314	2.35	3.14	£4,878	£6,229

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT5 treatment-experienced cirrhotic

Table 164: Base-case results: GT5 treatment-experienced cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.27	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	11.54	[redacted]	£6,616	2.28	1.36	£4,849	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	16.76	[redacted]	£11,617	7.49	4.85	£2,395	£2,395
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	13.06	[redacted]	£30,025	3.79	2.43	£12,376	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.2.10 GT6 overall

GT6 treatment-naïve non-cirrhotic

Table 165: Base-case results: GT6 treatment-naïve non-cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	19.09	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	20.45	[redacted]	£4,553	1.35	1.57	£2,895	£2,895
Sofosbuvir/velpatasvir (12 wks)	[redacted]	21.91	[redacted]	£14,992	2.82	3.58	£4,192	£5,212

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT6 treatment-naïve cirrhotic

Table 166: Base-case results: GT6 treatment-naïve cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.36	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	11.79	[redacted]	£7,552	2.43	1.45	£5,191	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	17.45	[redacted]	£12,819	8.10	5.21	£2,462	£2,462
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	13.45	[redacted]	£31,043	4.09	2.60	£11,920	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT6 treatment-experienced non-cirrhotic

Table 167: Base-case results: GT6 treatment-experienced non-cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	18.28	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	19.43	[redacted]	£4,344	1.15	1.38	£3,152	£3,152
Sofosbuvir/velpatasvir (12 wks)	[redacted]	20.64	[redacted]	£15,314	2.35	3.14	£4,878	£6,229

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT6 treatment-experienced cirrhotic

Table 168: Base-case results: GT6 treatment-experienced cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.27	[redacted]					
Peg-IFN + RBV (48 wks)	[redacted]	11.54	[redacted]	£6,616	2.28	1.36	£4,849	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	16.76	[redacted]	£11,617	7.49	4.85	£2,395	£2,395
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	13.06	[redacted]	£30,025	3.79	2.43	£12,376	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.2.11 Decompensated cirrhosis

DCC treatment-naïve

Table 169: Base-case results: DCC treatment-naïve (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Sofosbuvir/velpatasvir + RBV	[redacted]	7.65	[redacted]					
Ledipasvir/sofosbuvir + RBV (12 wks)	[redacted]	7.35	[redacted]	£7,329	-0.30	-0.16	Dominated	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

DCC treatment-experienced

Table 170: Base-case results: DCC treatment-experienced (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Sofosbuvir/velpatasvir + RBV	[redacted]	7.43	[redacted]					
Ledipasvir/sofosbuvir + RBV (12 wks)	[redacted]	7.14	[redacted]	£7,493	-0.29	-0.15	Dominated	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.7.3 *Clinical outcomes from the model*

Model outputs by clinical outcome are presented in the tables below for each treatment regimen for an example population (GT1, treatment-naïve cirrhotic cohort). An example population is provided given the large number of populations considered within the submission. LYs and QALYs have been discounted at a rate of 3.5% and assumed a time horizon of patients reaching 100 years of age. Across the modelled population significant improvements in health outcomes are noted compared with the comparators, with reductions in long-term complications, such as DCC, HCC, LT, and mortality (Table 171).

SVR data derived from clinical trials and presented in data input tables in Section 5.6.1 (patient-group specific inputs) was not transformed in any way and the model assumed no mortality while on treatment. As such, the proportion of patients achieving SVR as predicted by the model will be the same as the SVR data inputs.

Markov traces showing the number of patients in the cohort in each health state over time are presented in Appendix 18. Markov traces are provided for GT1, treatment-naïve cirrhotic cohort as an example. The Markov trace indicates that patients receiving SOF/VEL therapy spend more time in the SVR health states compared with the other treatments. The majority of QALYs for SOF/VEL regimens are accrued in these health states.

QALYs in each cycle are accrued by multiplying the number of patients in each health state by the utility for that state and applying discounting. To calculate the ICER, QALYs are then summed across the time horizon of the analysis. Markov traces, showing QALYs accrued in the cohort in each health state over time, are provided in Appendix 18, using GT1 treatment-naïve cirrhotic as an example.

Table 171: Summary of health outcomes in GT1 treatment-naïve cirrhotic (number of events/LY/QALY)

	CC/ 10,000 pt	DCC/ 10,000 pt	HCC/ 10,000 pt	Liver transplant/ 10,000 pt	Deaths/ 10,000 pt	LYs gained (discounted)/ pt	QALYs gained (discounted)/ pt
SOF/VEL (12 wks)	0	1,795	3,914	114	9,956	17.34	10.11
LDV/SOF (12 wks)	0	1,891	4,028	121	9,958	16.98	9.88
SOF+Peg-IFN+RBV (12 wks)	0	2,185	4,374	140	9,964	15.91	9.16
SMV+Peg-IFN+RBV (RGT)	0	2,628	4,891	170	9,973	14.40	8.16
Peg-IFN+RBV (48 wks)	0	3,434	5,840	225	9,989	11.68	6.36
No treatment	0	3,962	6,472	259	10,000	9.36	4.98

CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV, ledipasvir; LY, life years; Peg-IFN, pegylated interferon; pt, patient; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; VEL, velpatasvir.

5.7.4 *Disaggregated results of the base-case incremental cost effectiveness analysis*

Disaggregated QALYs by health state and disaggregated costs by category of costs are provided in Table 172 and Table 174, respectively for the example population of GT1 treatment-naïve, cirrhotic.

A higher number of QALYs are gained with the SOF/VEL regimen. This is explained by the fact that more patients are cured with SOF/VEL (that is, more patients reach the SVR health state which is associated with increased utility values), and consequently fewer patients progress to the more severe health state where HRQL is expected to decrease. This highlights the overall positive impact of SOF/VEL on a patient's quality of life.

Patients treated with SOF/VEL have lower costs associated with off-treatment health states compared with those in the comparator arms in the majority of cases. This is a consequence of better efficacy of SOF/VEL, which means that fewer patients will suffer from more advanced health states and complications. SOF/VEL is also associated with lower on-treatment costs compared with some regimens due to the lower acquisition costs and reduction in monitoring required.

Table 172: Summary of QALY gain by health state in GT1 treatment-naïve cirrhotic

	CC on treatment	CC	CC with SVR	DCC	HCC	Liver transplant	Post-liver transplant	Total QALYs (undiscounted)
SOF/VEL (12 wks)	0.14	0.21	16.27	0.24	0.39	0.01	0.07	17.33
LDV/SOF (12 wks)	0.14	0.43	15.54	0.25	0.41	0.01	0.07	16.85
SOF+Peg-IFN+RBV (12 wks)	0.12	1.08	13.34	0.29	0.44	0.01	0.09	15.37
SMV+Peg-IFN+RBV (RGT)	0.24	2.08	9.94	0.35	0.49	0.01	0.12	13.22
Peg-IFN+RBV (48 wks)	0.39	3.87	3.87	0.46	0.59	0.01	0.16	9.35
No treatment	0.07	5.04	-	0.53	0.65	0.01	0.19	6.49

CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV, ledipasvir; LY, life years; Peg-IFN, pegylated interferon; pt, patient; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

Table 173: Summary of disaggregation of model costs by health state in GT1 treatment-naïve cirrhotic (per patient, undiscounted, anticipated list price for SOF/VEL)

	CC on treatment	CC	CC with SVR	DCC	HCC	Liver transplant	Post-liver transplant
Sofosbuvir/velpatasvir (12 wks)	£41,285	£595	£14,143	£6,583	£9,780	£970	£647
Ledipasvir/sofosbuvir (12 wks)	£41,201	£1,209	£13,509	£6,944	£10,062	£1,024	£693
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	£39,569	£3,067	£11,593	£8,037	£10,915	£1,189	£833
Simeprevir + Peg-IFN2a + RBV (RGT)	£31,073	£5,893	£8,639	£9,698	£12,216	£1,446	£1,043
Peg-IFN2a + RBV (48 wks)	£12,819	£10,991	£3,362	£12,740	£14,620	£1,919	£1,424
No treatment	£338	£14,315	£0	£14,638	£16,059	£2,179	£1,678

CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV, ledipasvir; LY, life years; Peg-IFN, pegylated interferon; pt, patient; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

Table 174: Summary of disaggregation of model costs by health resource type in GT1 treatment-naïve cirrhotic (discounted, anticipated list price for SOF/VEL)

	Total/ pt	Pharmacy/ pt	Hospitalisation / pt	Outpatient costs			Treatment (Drug, AE's, Monitoring)					
				Total/pt	Emergency /pt	Ambulatory / pt	Total/ pt	Treatment/ pt	Monitoring cirrhotic/ pt	AE /pt		
										Total cost/ pt	AE drug/ pt	AE management/ pt
SOF/VEL (12 wks)	£59,675	£4,525	£4,525	£9,049	£4,525	£4,525	£41,285	£38,881	£2,404	£0	£0	£0
LDV/SOF (12 wks)	£60,349	£4,707	£4,707	£9,415	£4,707	£4,707	£41,201	£38,798	£2,403	£0	£0	£0
SOF+Peg-IFN+RBV (12 wks)	£61,014	£5,261	£5,261	£10,521	£5,261	£5,261	£39,569	£37,072	£2,396	£102	£73	£29
SMV+Peg-IFN+RBV (RGT)	£55,825	£6,057	£6,057	£12,113	£6,057	£6,057	£31,073	£27,430	£3,508	£135	£97	£38
Peg-IFN+RBV (48 wks)	£43,577	£7,503	£7,503	£15,006	£7,503	£7,503	£12,819	£8,329	£4,279	£211	£155	£56
No treatment	£35,790	£8,635	£8,635	£17,269	£8,635	£8,635	£338	£0	£338	£0	£0	£0

LDV, ledipasvir; Peg-IFN, pegylated interferon; pt, patient; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; VEL, velpatasvir.
Costs of post-liver transplant year 1 & 2 were not broken down by pharmacy, hospitalisation and outpatient (emergency & ambulatory) costs; All costs are discounted (3.5%).

5.8 *Sensitivity analyses*

5.8.1 *Probabilistic sensitivity analysis*

5.8.1.1 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 175 below.

Table 175: Generic PSA input values

Variable	Distribution and parameters	Source
Health state costs		
Non-cirrhotic disease	Gamma; α=61.5; β=5.3	Wright, 2006 (167)
Cirrhotic disease	Gamma; α=61.5; β=25.4	Wright, 2006 (165)
Decompensated cirrhosis	Gamma; α=61.5; β=203.5	Wright, 2006 (165)
Non-cirrhotic disease - SVR	Gamma; α=61.5; β=4.0	Grishchenko, 2009 (164)
Cirrhotic disease - SVR	Gamma; α=61.5; β=8.3	Grishchenko, 2009 (164)
Decompensated cirrhosis - SVR	Gamma; α=61.5; β=203.5	Assumption
Hepatocellular carcinoma	Gamma; α=61.5; β=181.4	Wright, 2006 (165)
Liver transplant	Gamma; α=61.5; β=1386.0	Longworth, 2014 (188)
Post-liver transplant – Year 1	Gamma; α=61.5; β=456.7	Longworth, 2014 (188)
Post-liver transplant – Year 2	Gamma; α=61.5; β=68.2	Longworth, 2014 (188)
Utility weights		
Non-cirrhotic - without treatment	Beta; α=681.8; β=225.7	Wright, 2006 (UK mild HCV trial) (165)

Variable	Distribution and parameters	Source
Cirrhotic - without treatment	Beta; α=46.6; β=38.1	Wright, 2006 (UK mild HCV trial) (165)
Decompensated cirrhosis - without treatment	Beta; α=123.8; β=151.3	Wright, 2006 (UK mild HCV trial) (165)
SVR - Utility increment	Gamma; α=0.8; β=0.1	Vera-Llonch et al, 2013 (185)
Hepatocellular carcinoma	Beta; α=123.8; β=151.3	Wright, 2006 (UK mild HCV trial) (165)
Liver transplant	Beta; α=123.8; β=151.3	Wright, 2006 (UK mild HCV trial) (165)
Post-liver transplant	Beta; α=33.3; β=16.4	Wright, 2006 (UK mild HCV trial) (165)
Transition probabilities		
From compensated cirrhosis to decompensated cirrhosis	Beta; α=32.5; β=710.0	Cardoso, 2010 (50) - 95% CI calculated based on Cardoso 2010 (50)
From compensated cirrhosis to HCC	Beta; α=50, β=744	Cardoso, 2010 (50) - 95% CI calculated based on Cardoso 2010 (50)
From compensated cirrhosis with SVR to decompensated cirrhosis	Beta; α=3.7; β=577.4	Cardoso, 2010 (50) - 95% CI calculated based on Cardoso 2010 (50)
From compensated cirrhosis with SVR to HCC	Beta; α=7; β=502	Cardoso, 2010 (50) - 95% CI calculated based on Cardoso 2010 (50)
From decompensated cirrhosis to HCC	Beta; α=50 β=744	Cardoso, 2010 (50) - 95% CI calculated based on Cardoso 2010 (50) Assumed equal to transition probability of compensated cirrhosis to HCC
From decompensated cirrhosis to liver transplant	Beta; α=15; β=667	Siebert, 2005 (182)
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 (183) - Beta parameters from Shepherd et al 2007 (162)
From liver transplant to death	Beta; α=16.3; β=61.2	Bennett, 1997 (184) - Beta parameters from Shepherd et al 2007 (162)
From post-liver transplant to death	Beta; α=22.9; β=378.9	Bennett, 1997 (184) - Beta parameters from Shepherd et al 2007 (162)

HCC, Hepatocellular carcinoma; SVR, Sustained virologic response

Indication- and genotype-specific PSA inputs

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

TP from non-cirrhotic to cirrhotic were assumed to follow a beta distribution, as presented in Table 176. 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 176: Genotype-specific PSA inputs - TP from 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

Source: Kanwal 2014 (172).

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.

5.8.1.2 Results

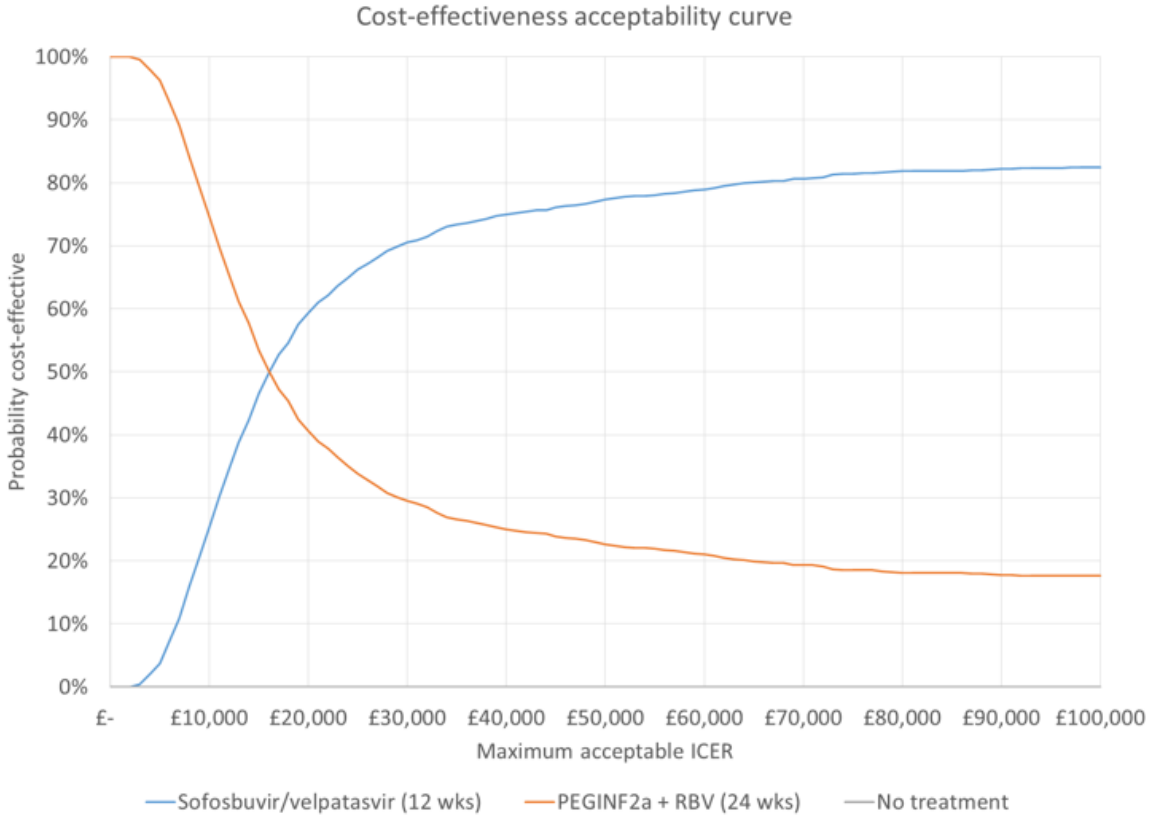
GT3 overall

GT3 treatment-naïve non-cirrhotic

Table 177: Probability of cost-effectiveness: GT3 treatment-naïve non-cirrhotic (discounted price)

Threshold	Probability of cost-effectiveness (%)
£20,000	59
£30,000	71

Figure 18: Multiple CEACs: GT3 treatment-naïve non-cirrhotic (discounted price)

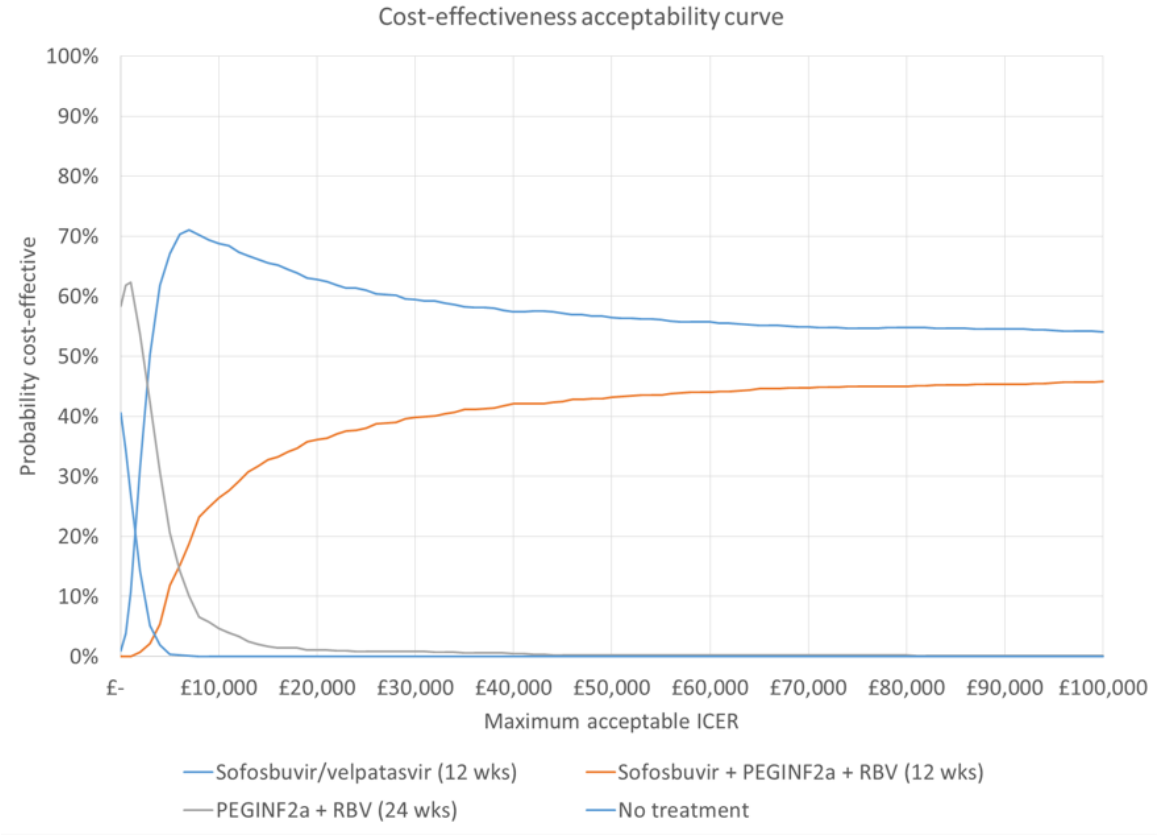


GT3 treatment-naïve cirrhotic

Table 178: Probability of cost-effectiveness: GT3 treatment-naïve cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	63
£30,000	59

Figure 19: Multiple CEACs: GT3 treatment-naïve cirrhotic (discounted price)



GT3 treatment-experienced non-cirrhotic

Table 179: Probability of cost-effectiveness: GT3 treatment-experienced non-cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	64
£30,000	57

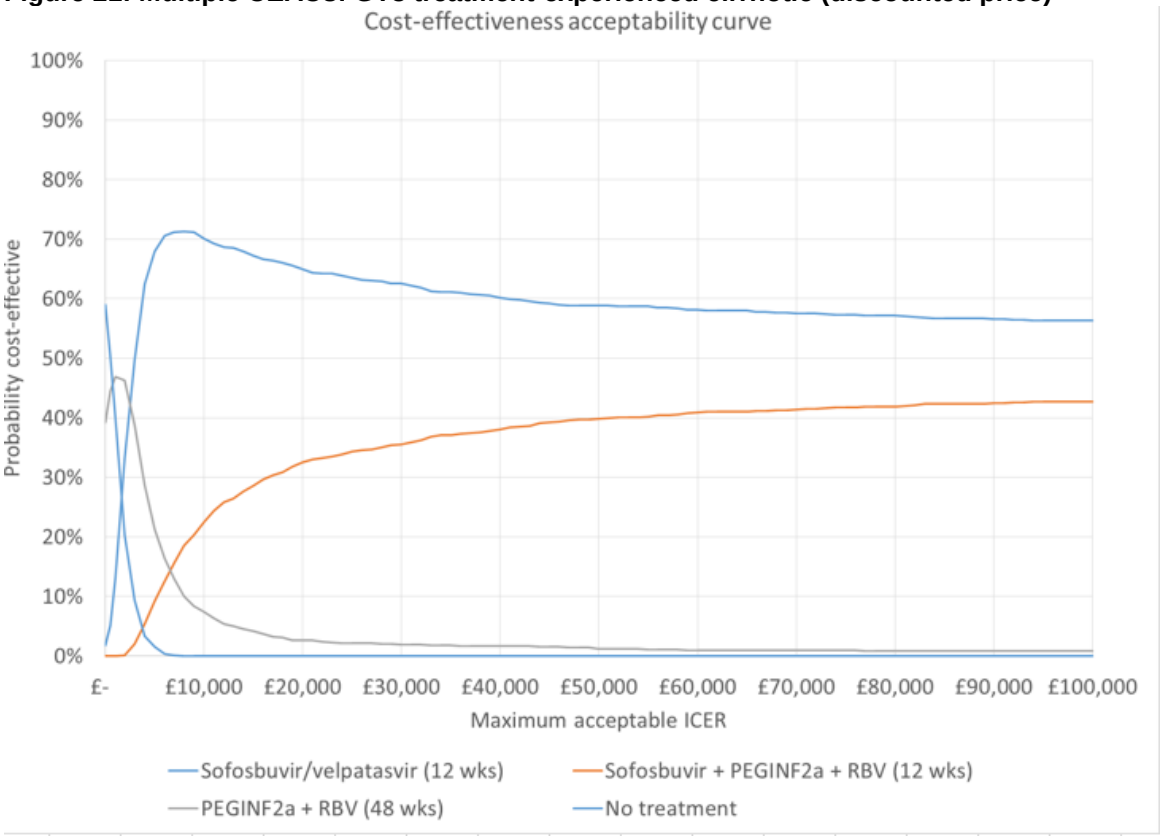
Figure 20: Multiple CEACs: GT3 treatment-experienced non-cirrhotic (discounted price)

GT3 treatment-experienced cirrhotic

Table 180: Probability of cost-effectiveness: GT3 treatment-experienced cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	65
£30,000	63

Figure 21: Multiple CEACs: GT3 treatment-experienced cirrhotic (discounted price)



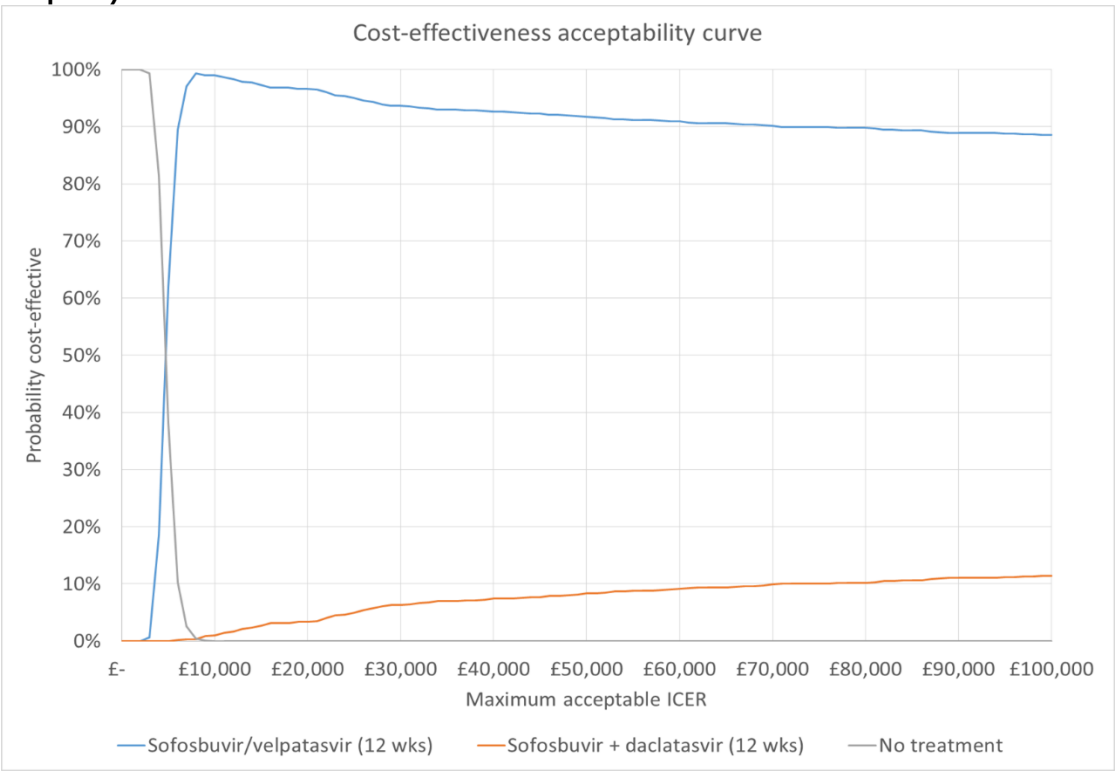
GT3 IFN-ineligible

GT3 treatment-naïve non-cirrhotic IFN-ineligible

Table 181: Probability of cost-effectiveness: GT3 treatment-naïve non-cirrhotic IFN-ineligible (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	97
£30,000	94

Figure 22: Multiple CEACs: GT3 treatment-naïve non-cirrhotic IFN-ineligible (anticipated list price)

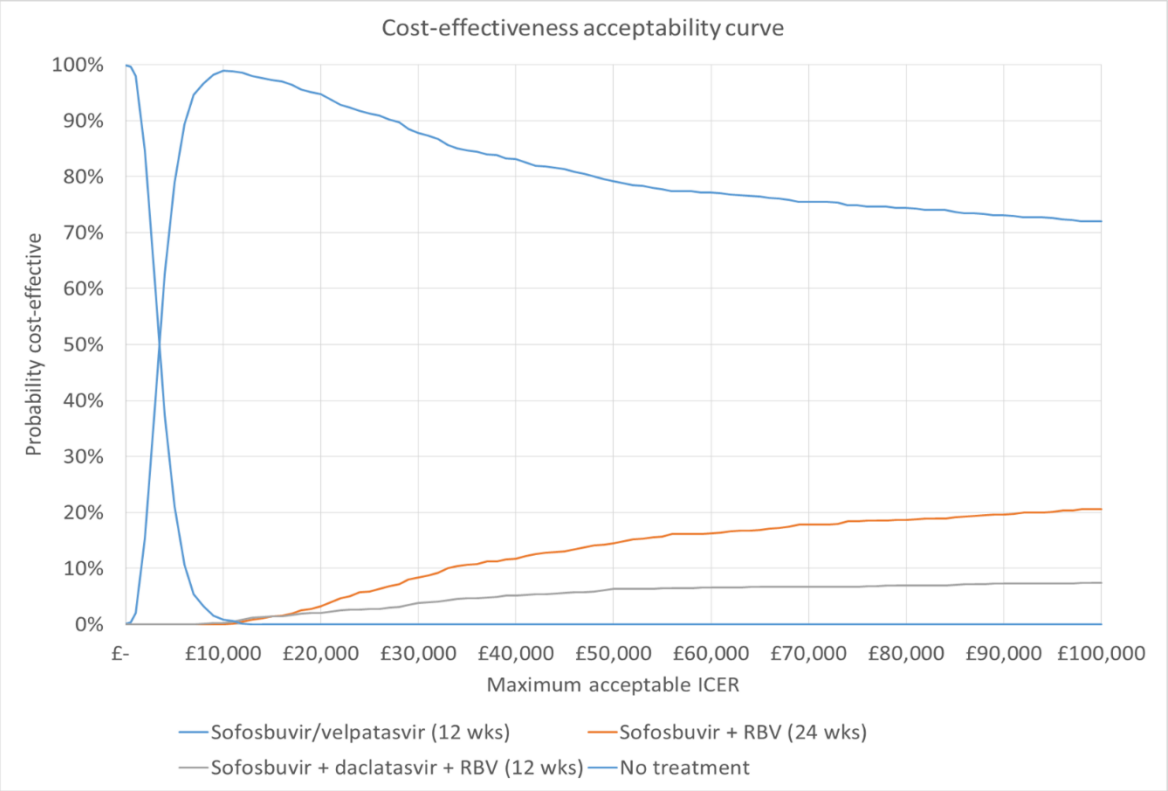


GT3 treatment-naïve cirrhotic IFN-ineligible

Table 182: Probability of cost-effectiveness: GT3 treatment-naïve cirrhotic IFN-ineligible (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	95
£30,000	88

Figure 23: Multiple CEACs: GT3 treatment-naïve cirrhotic IFN-ineligible (anticipated list price)

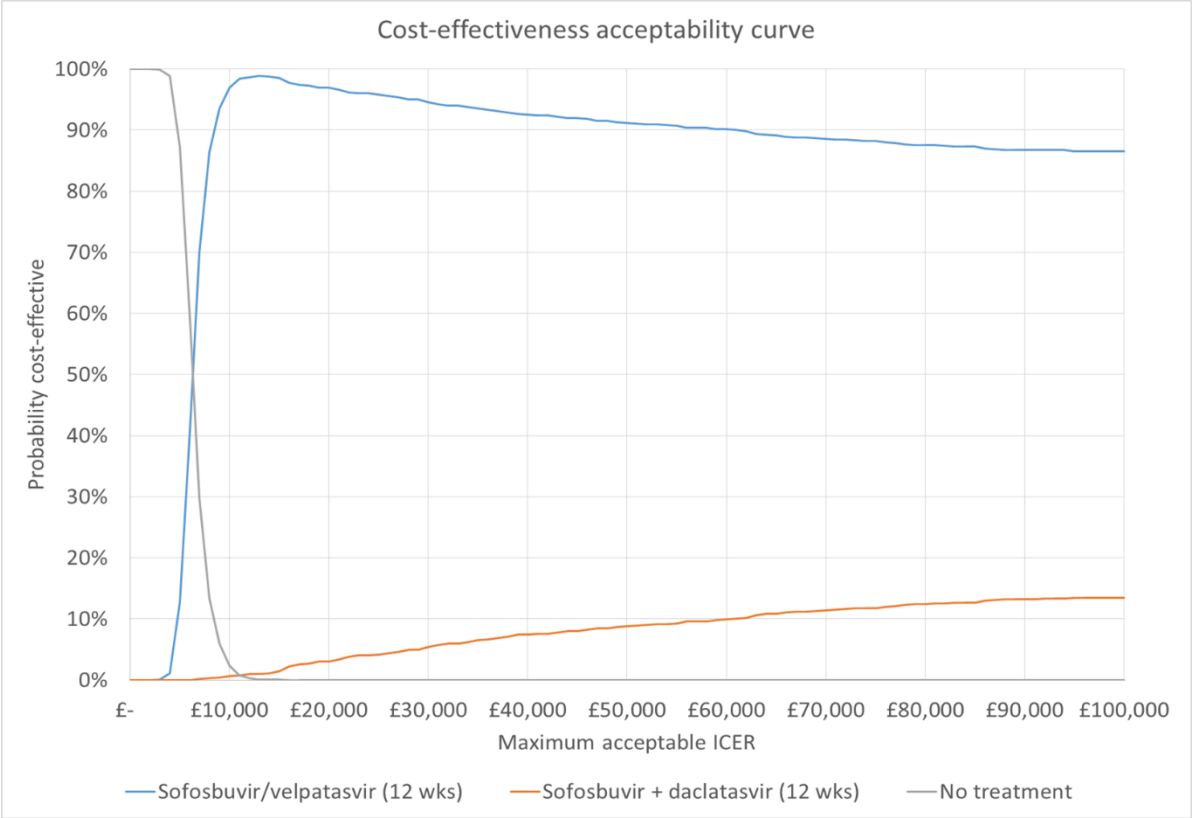


GT3 treatment-experienced non-cirrhotic IFN-ineligible

Table 183: Probability of cost-effectiveness: GT3 treatment-experienced non-cirrhotic IFN-ineligible (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	97
£30,000	95

Figure 24: Multiple CEACs: GT3 treatment-experienced non-cirrhotic IFN-ineligible (anticipated list price)

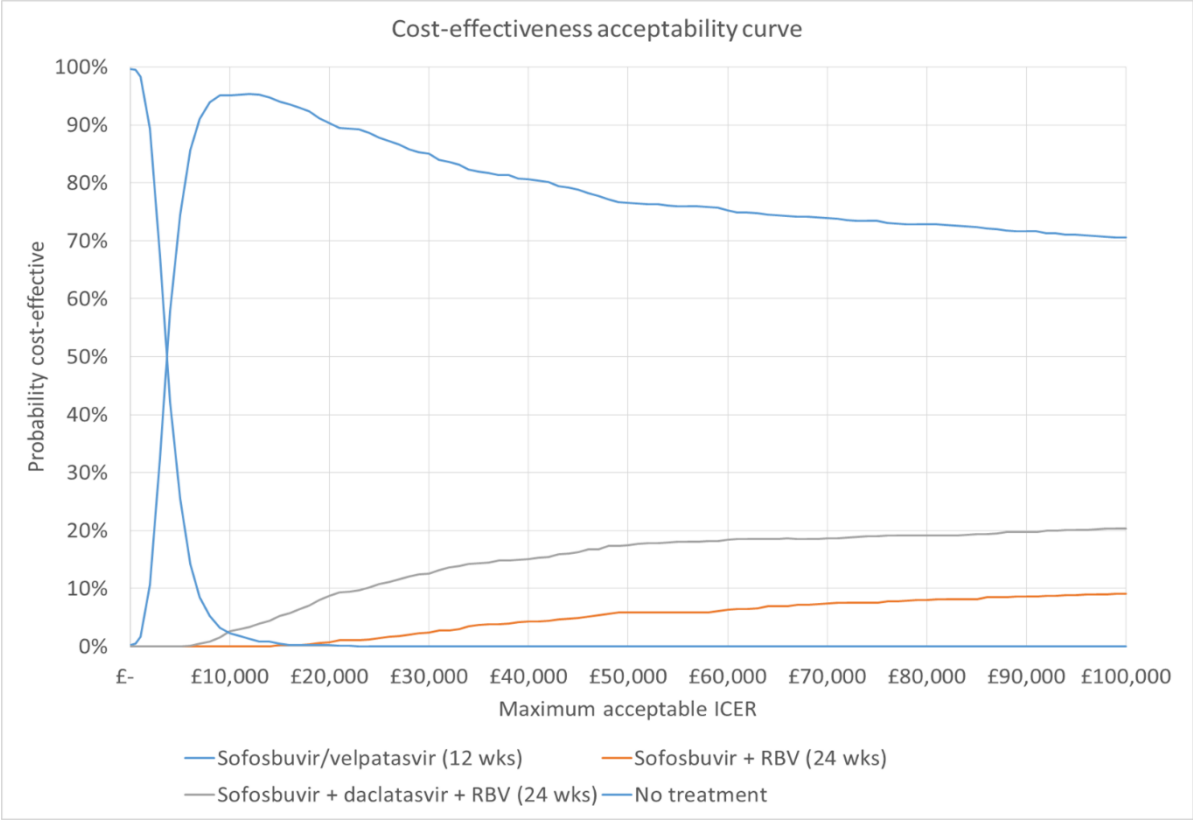


GT3 treatment-experienced cirrhotic IFN-ineligible

Table 184: Probability of cost-effectiveness: GT3 treatment-experienced cirrhotic IFN-ineligible (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	90
£30,000	85

Figure 25: Multiple CEACs: GT3 treatment-experienced cirrhotic IFN-ineligible (anticipated list price)



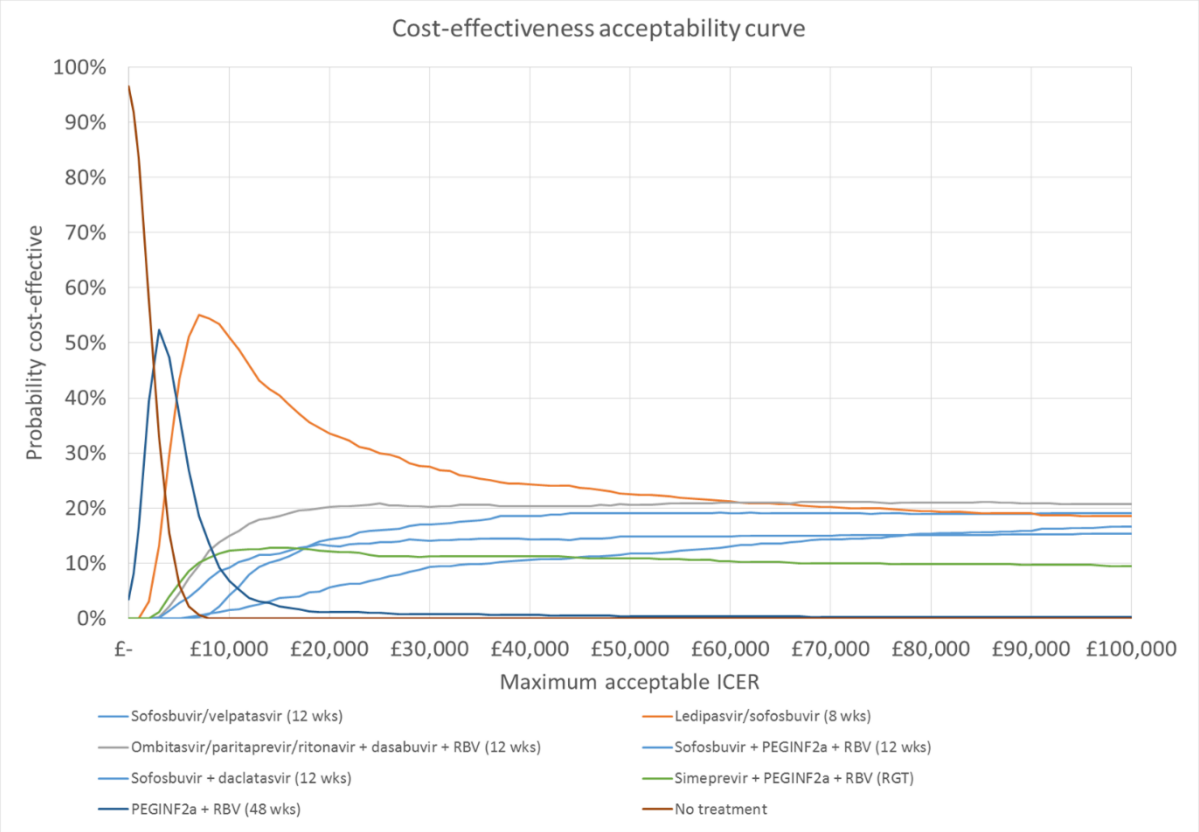
GT1a overall

GT1a treatment-naïve non-cirrhotic

Table 185: Probability of cost-effectiveness: GT1a treatment-naïve non-cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	14
£30,000	17

Figure 26: Multiple CEACs: GT1a treatment-naïve non-cirrhotic (anticipated list price)

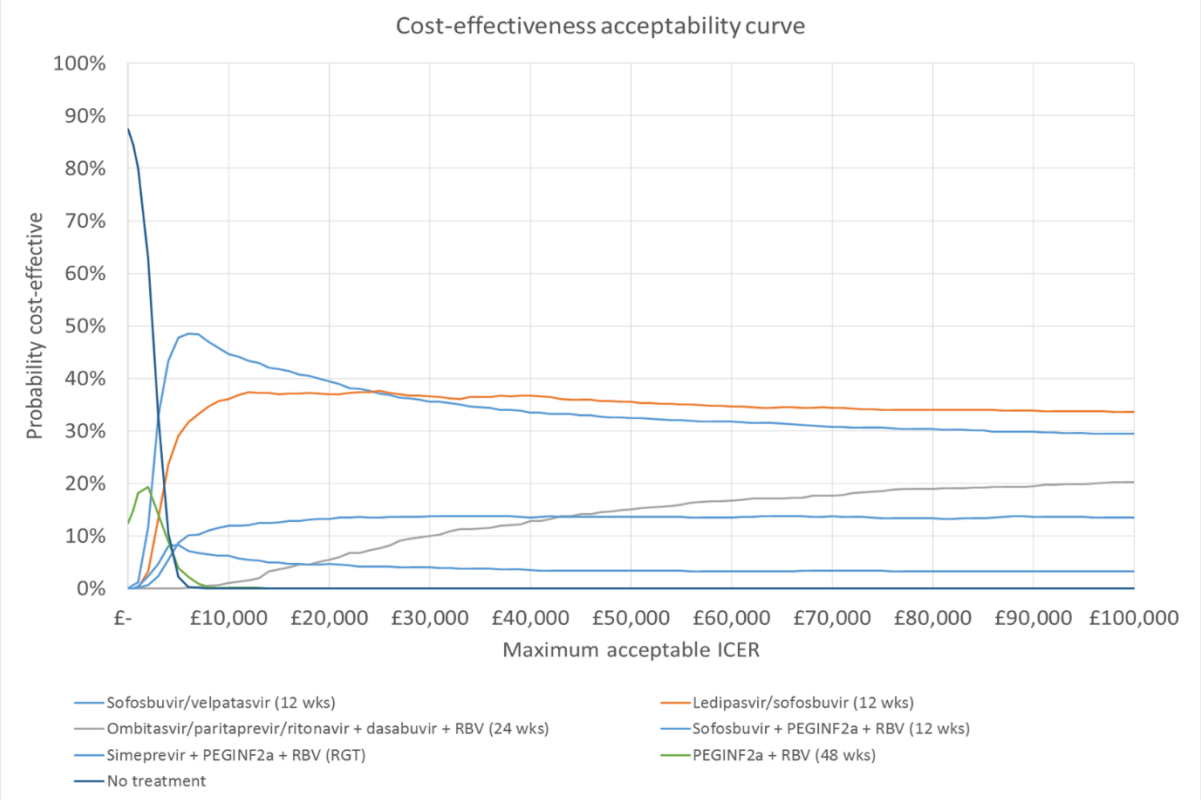


GT1a treatment-naïve cirrhotic

Table 186: Probability of cost-effectiveness: GT1a treatment-naïve cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	40
£30,000	36

Figure 27: Multiple CEACs: GT1a treatment-naïve cirrhotic (anticipated list price)

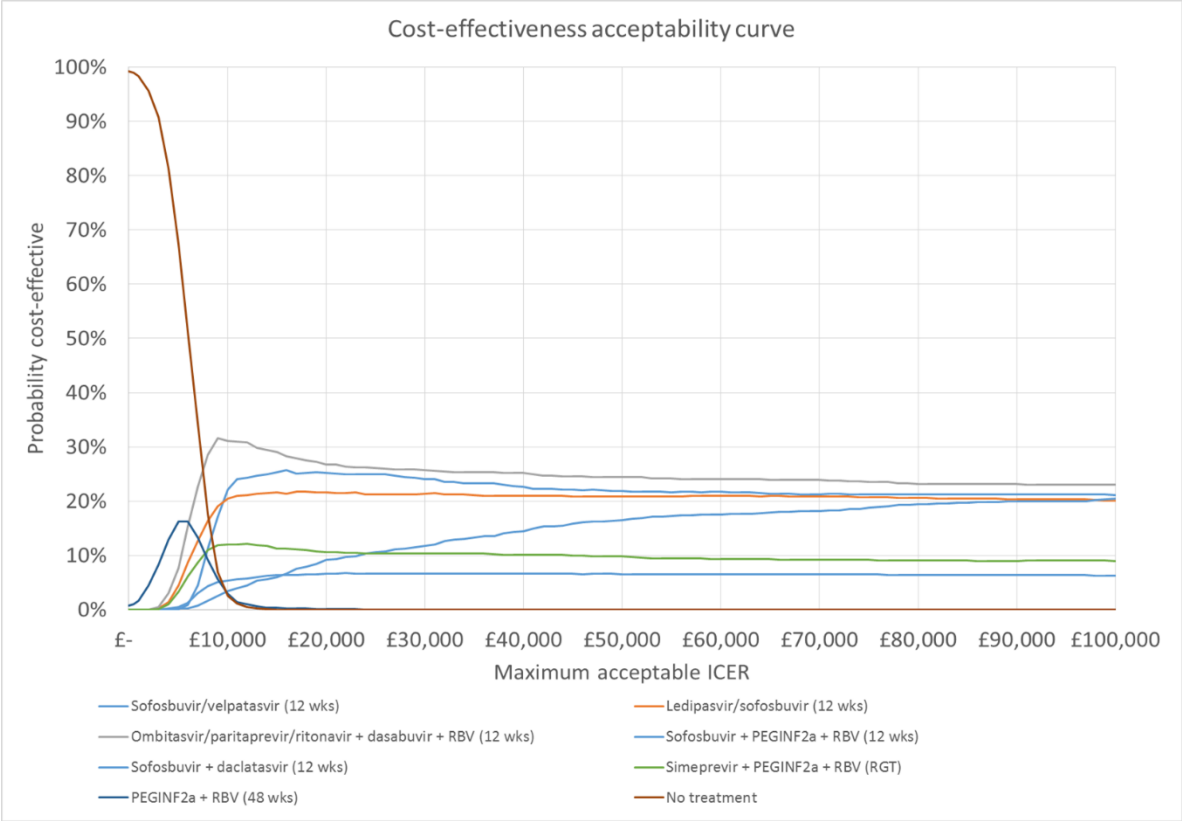


GT1a treatment-experienced non-cirrhotic

Table 187: Probability of cost-effectiveness: GT1a treatment-experienced non-cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	25
£30,000	24

Figure 28: Multiple CEACs: GT1a treatment-experienced non-cirrhotic (anticipated list price)

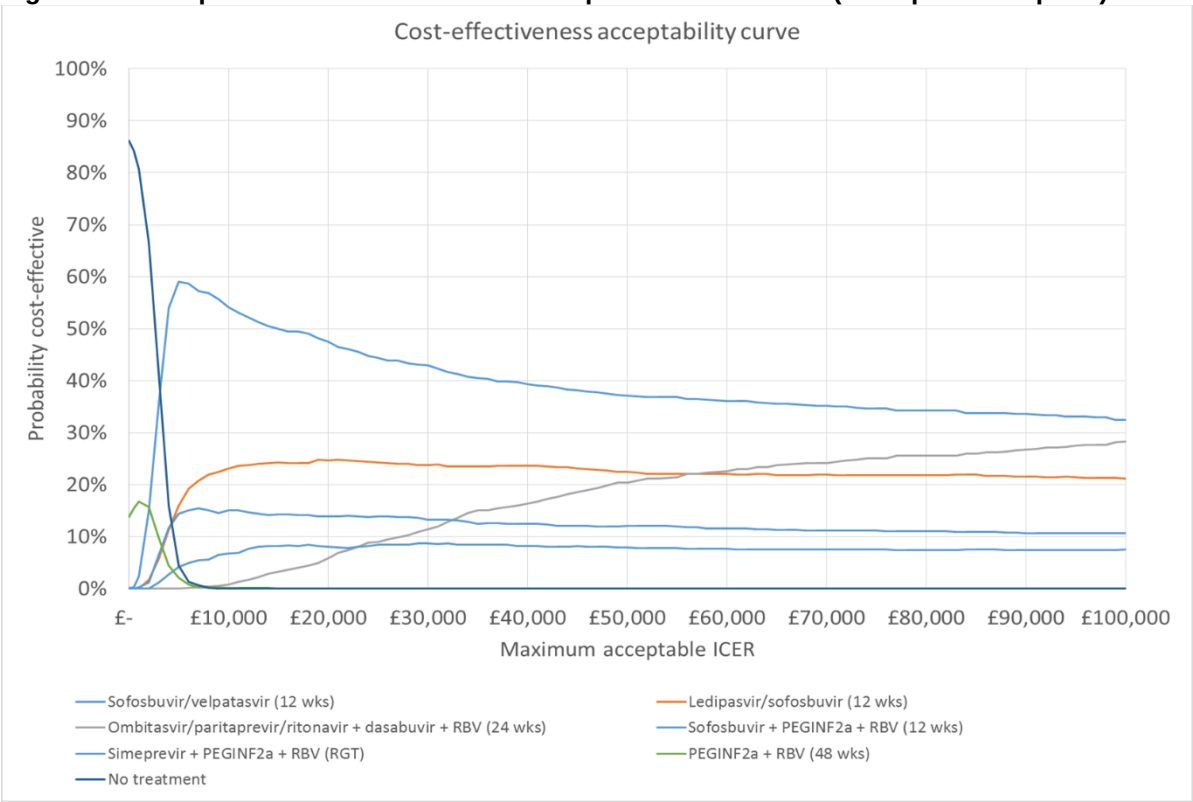


GT1a treatment-experienced cirrhotic

Table 188: Probability of cost-effectiveness: GT1a treatment-experienced cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	48
£30,000	43

Figure 29: Multiple CEACs: GT1a treatment-experienced cirrhotic (anticipated list price)



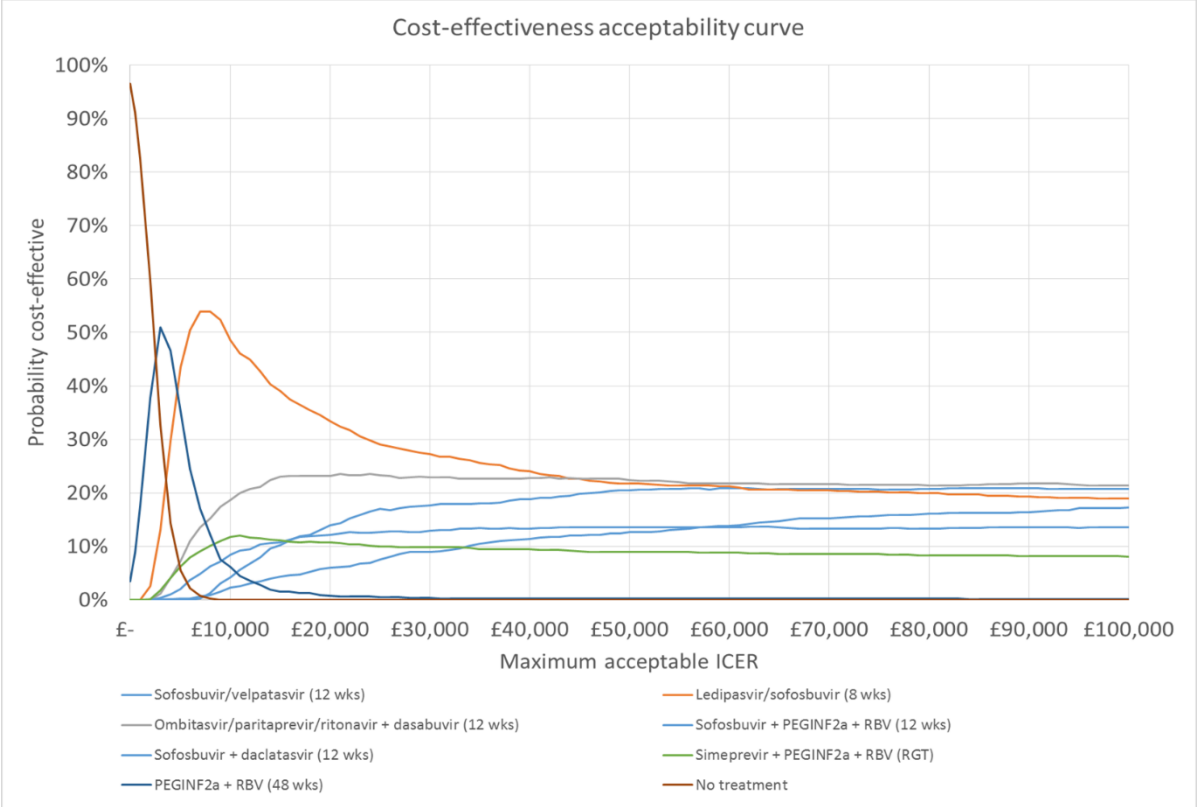
GT1b overall

GT1b treatment-naïve non-cirrhotic

Table 189: Probability of cost-effectiveness: GT1b treatment-naïve non-cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	14
£30,000	18

Figure 30: Multiple CEACs: GT1b treatment-naïve non-cirrhotic (anticipated list price)

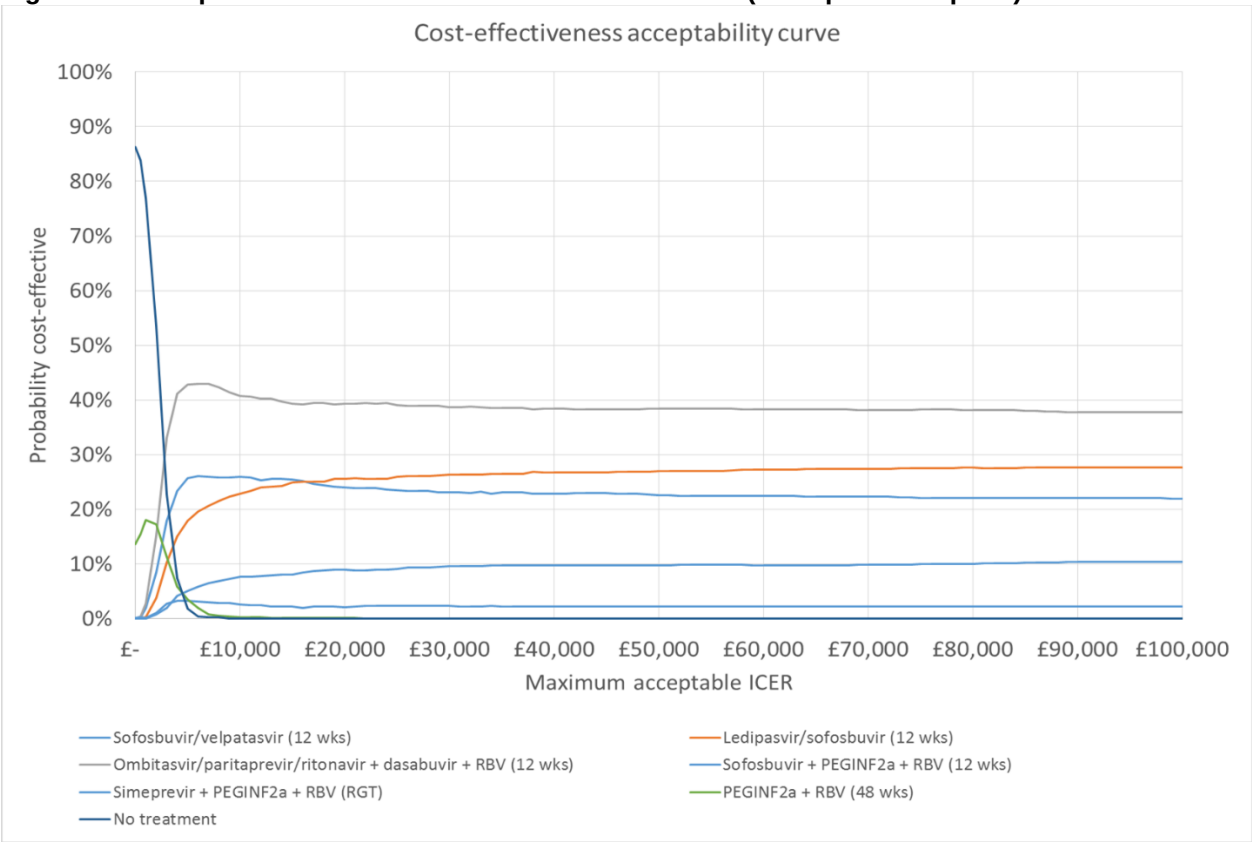


GT1b treatment-naïve cirrhotic

Table 190: Probability of cost-effectiveness: GT1b treatment-naïve cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	24
£30,000	23

Figure 31: Multiple CEACs: GT1b treatment-naïve cirrhotic (anticipated list price)

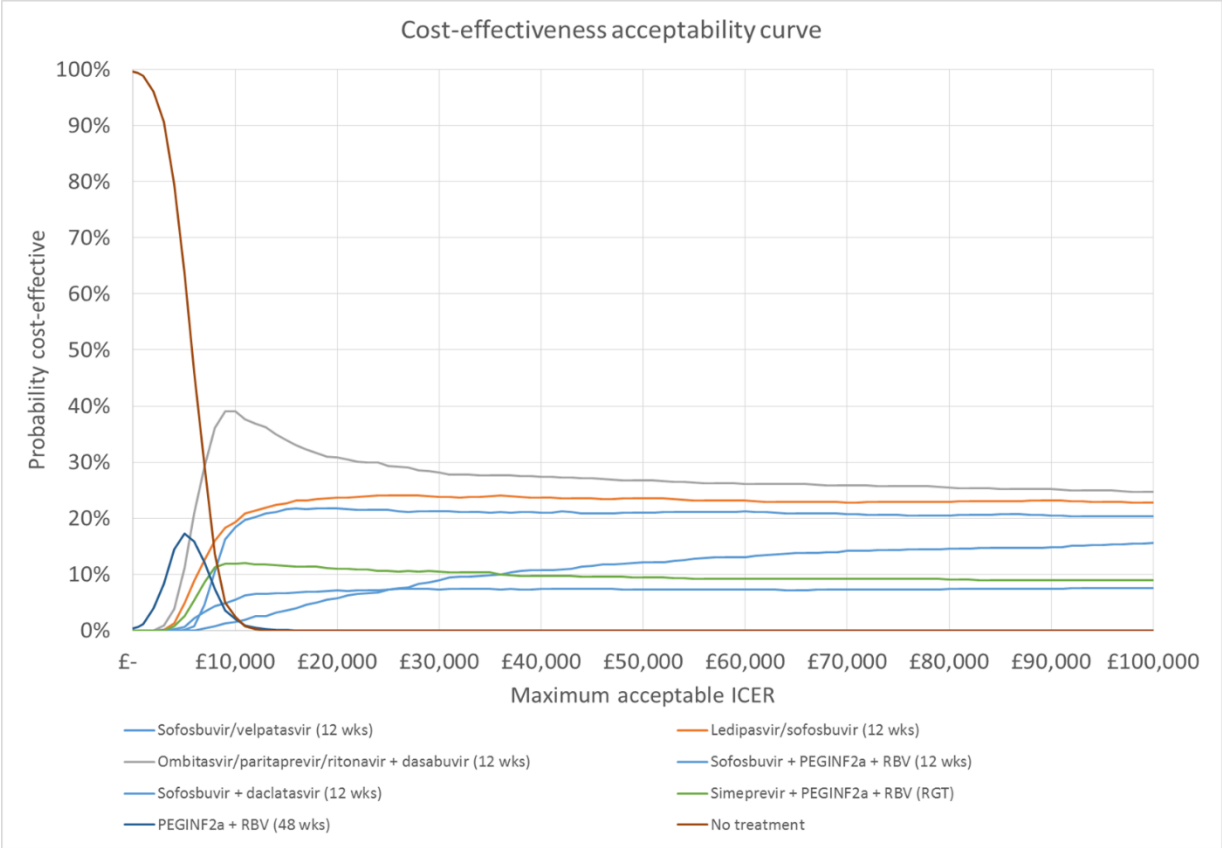


GT1b treatment-experienced non-cirrhotic

Table 191: Probability of cost-effectiveness: GT1b treatment-experienced non-cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	22
£30,000	21

Figure 32: Multiple CEACs: GT1b treatment-experienced non-cirrhotic (anticipated list price)

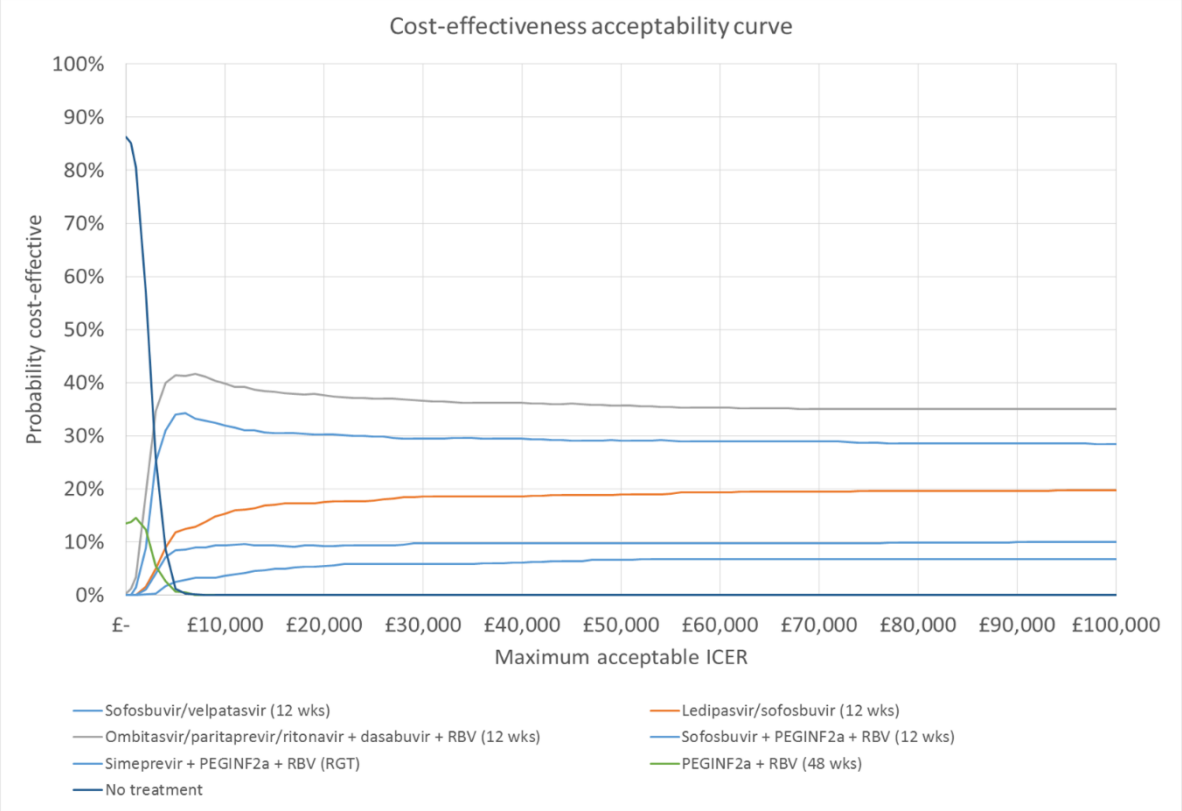


GT1b treatment-experienced cirrhotic

Table 192: Probability of cost-effectiveness: GT1b treatment-experienced cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	30
£30,000	29

Figure 33: Multiple CEACs: GT1b treatment-experienced cirrhotic (anticipated list price)



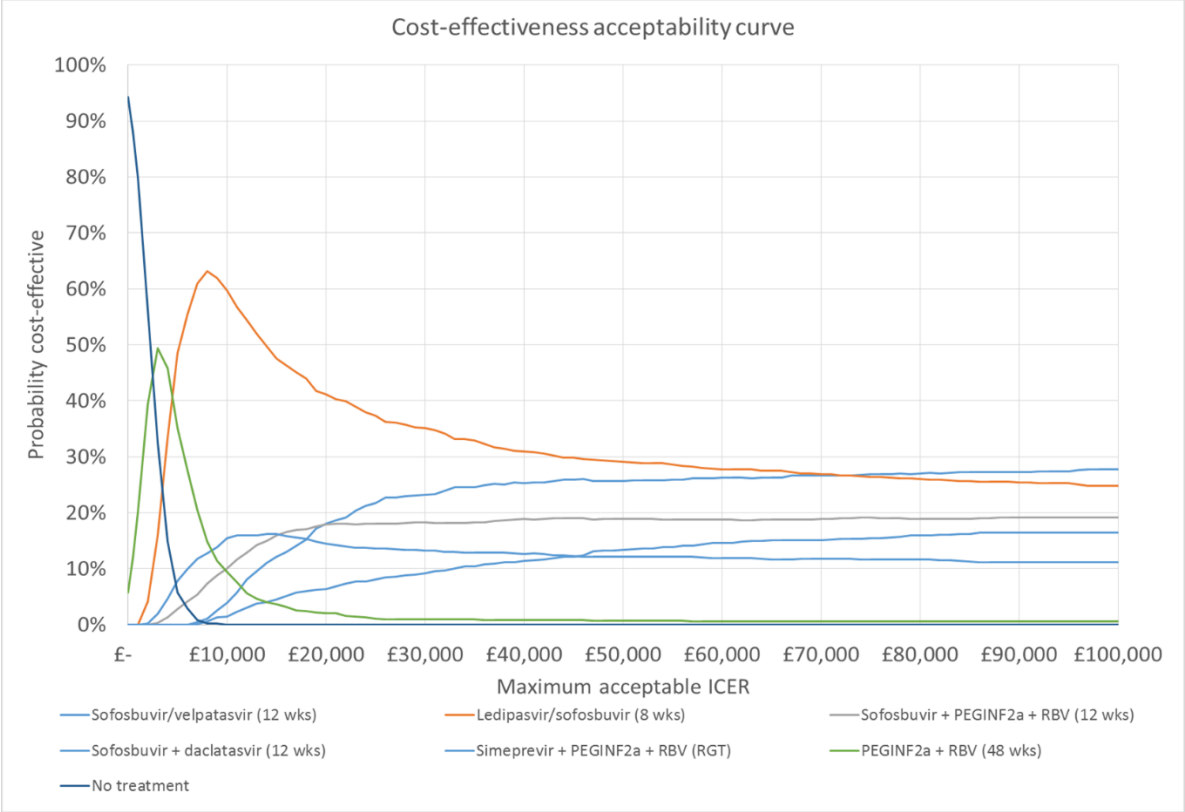
GT1 overall

GT1 treatment-naïve non-cirrhotic

Table 193: Probability of cost-effectiveness: GT1 treatment-naïve non-cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	18
£30,000	23

Figure 34: Multiple CEACs: GT1 treatment-naïve non-cirrhotic (anticipated list price)

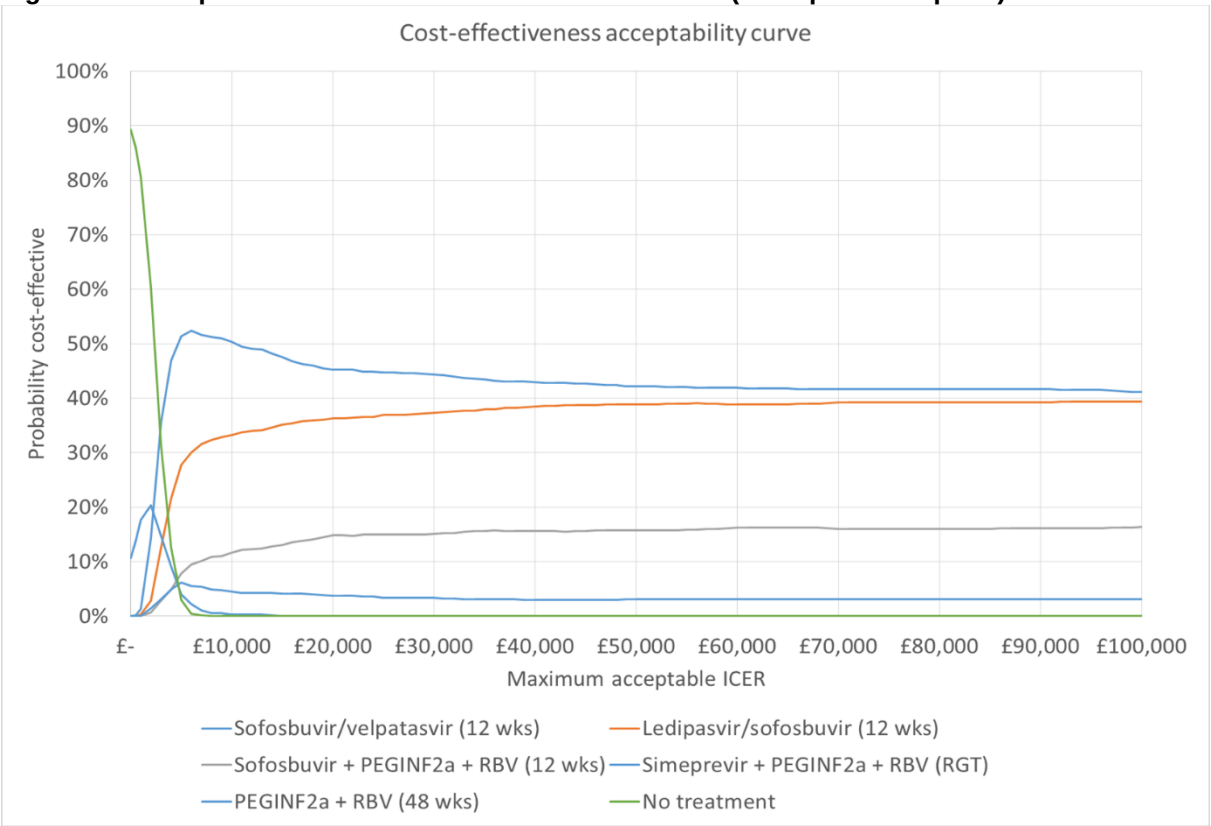


GT1 treatment-naïve cirrhotic

Table 194: Probability of cost-effectiveness: GT1 treatment-naïve cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	45
£30,000	44

Figure 35: Multiple CEACs: GT1 treatment-naïve cirrhotic (anticipated list price)

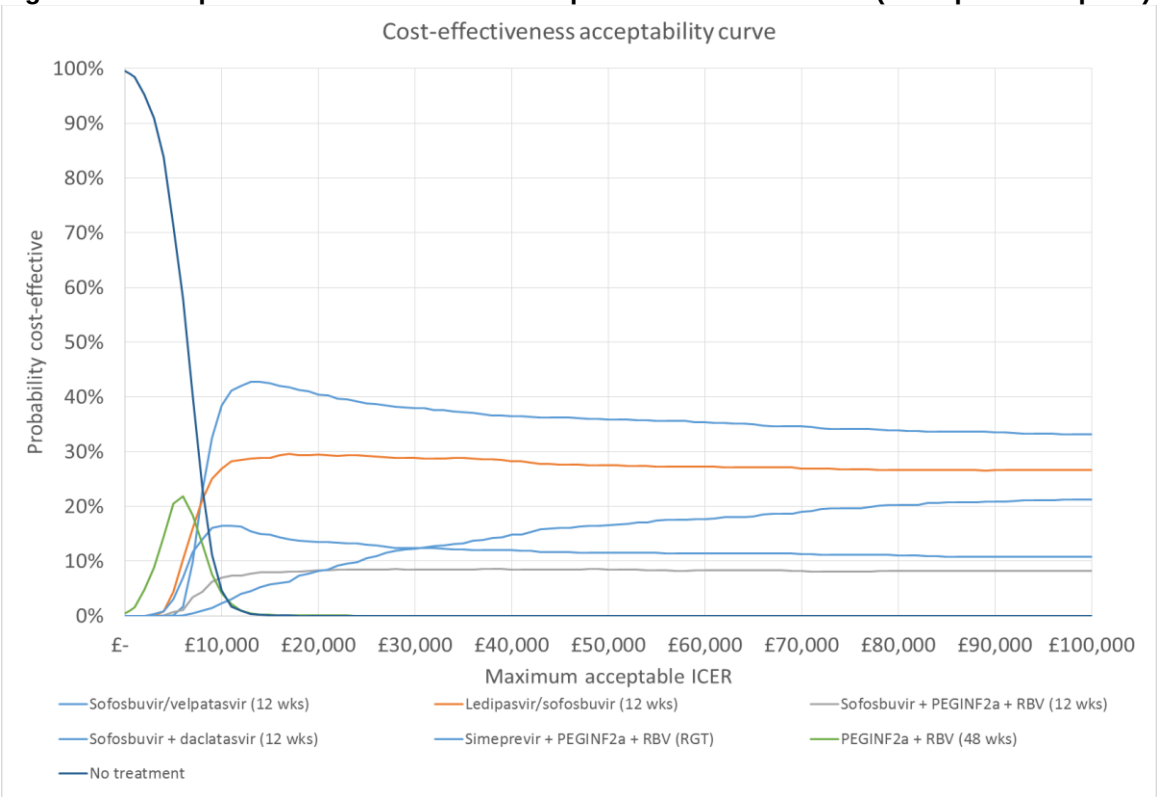


GT1 treatment-experienced non-cirrhotic

Table 195: Probability of cost-effectiveness: GT1 treatment-experienced non-cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	40
£30,000	38

Figure 36: Multiple CEACs: GT1 treatment-experienced non-cirrhotic (anticipated list price)



GT1 treatment-experienced cirrhotic

Table 196: Probability of cost-effectiveness: GT1 treatment-experienced cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	53
£30,000	50

Figure 37: Multiple CEACs: GT1 treatment-experienced cirrhotic (anticipated list price)

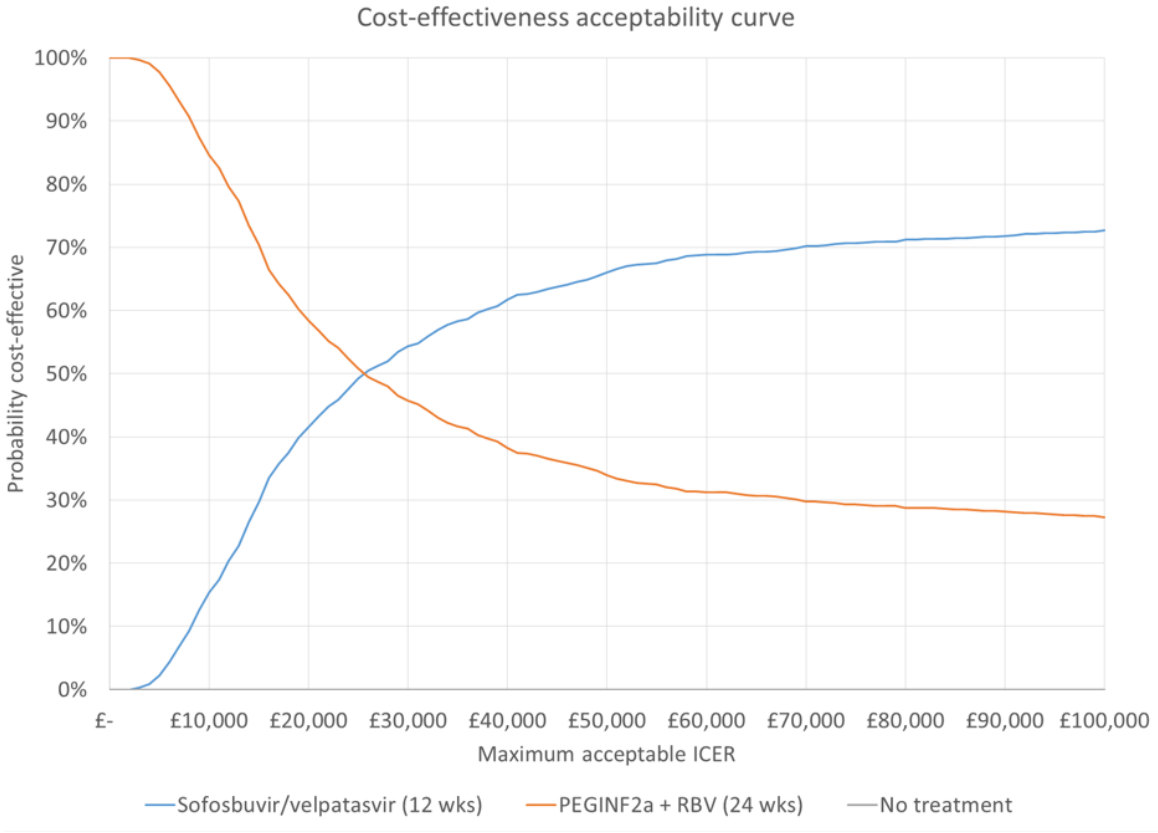
GT2 overall

GT2 treatment-naïve non-cirrhotic

Table 197: Probability of cost-effectiveness: GT2 treatment-naïve non-cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	42
£30,000	54

Figure 38: Multiple CEACs: GT2 treatment-naïve non-cirrhotic (discounted price)

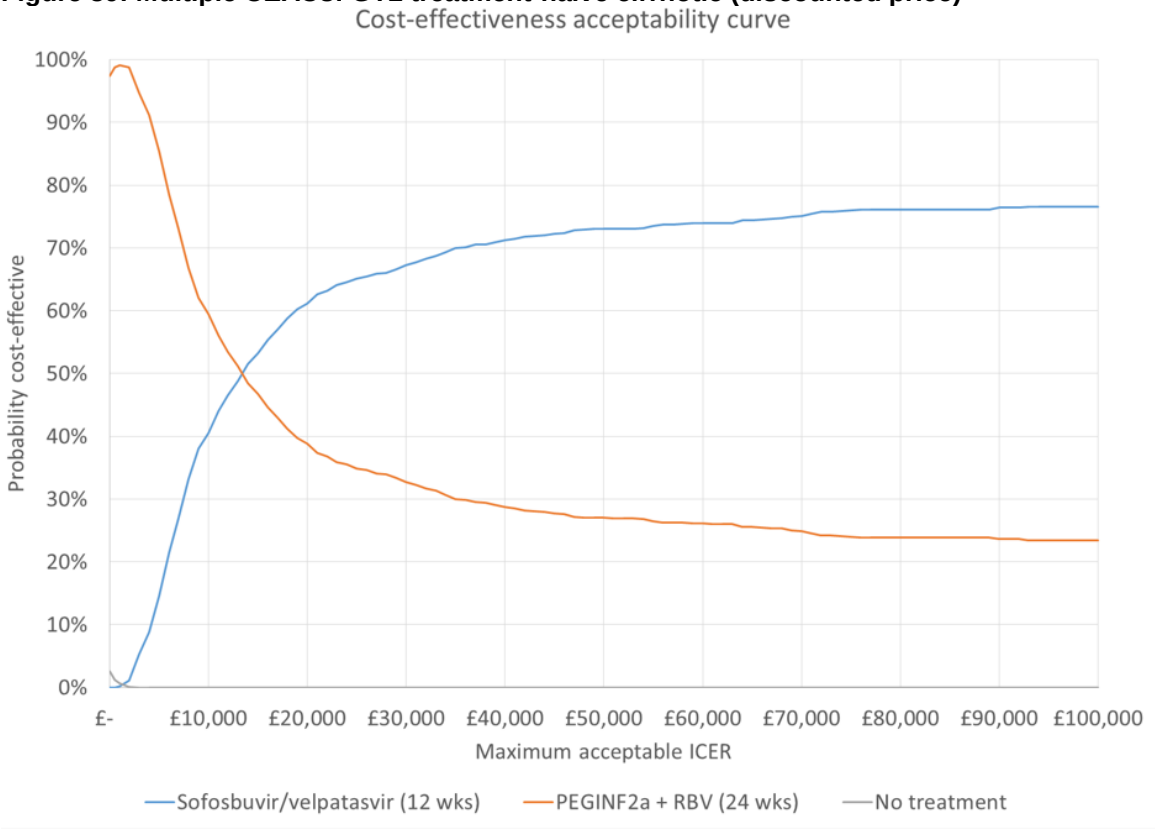


GT2 treatment-naïve cirrhotic

Table 198: Probability of cost-effectiveness: GT2 treatment-naïve cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	61
£30,000	67

Figure 39: Multiple CEACs: GT2 treatment-naïve cirrhotic (discounted price)



GT2 treatment-experienced non-cirrhotic

Table 199: Probability of cost-effectiveness: GT2 treatment-experienced non-cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	87
£30,000	83

Figure 40: Multiple CEACs: GT2 treatment-experienced non-cirrhotic (discounted price)

GT2 treatment-experienced cirrhotic

Table 200: Probability of cost-effectiveness: GT2 treatment-experienced cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	64
£30,000	61

Figure 41: Multiple CEACs: GT2 treatment-experienced cirrhotic (discounted price)

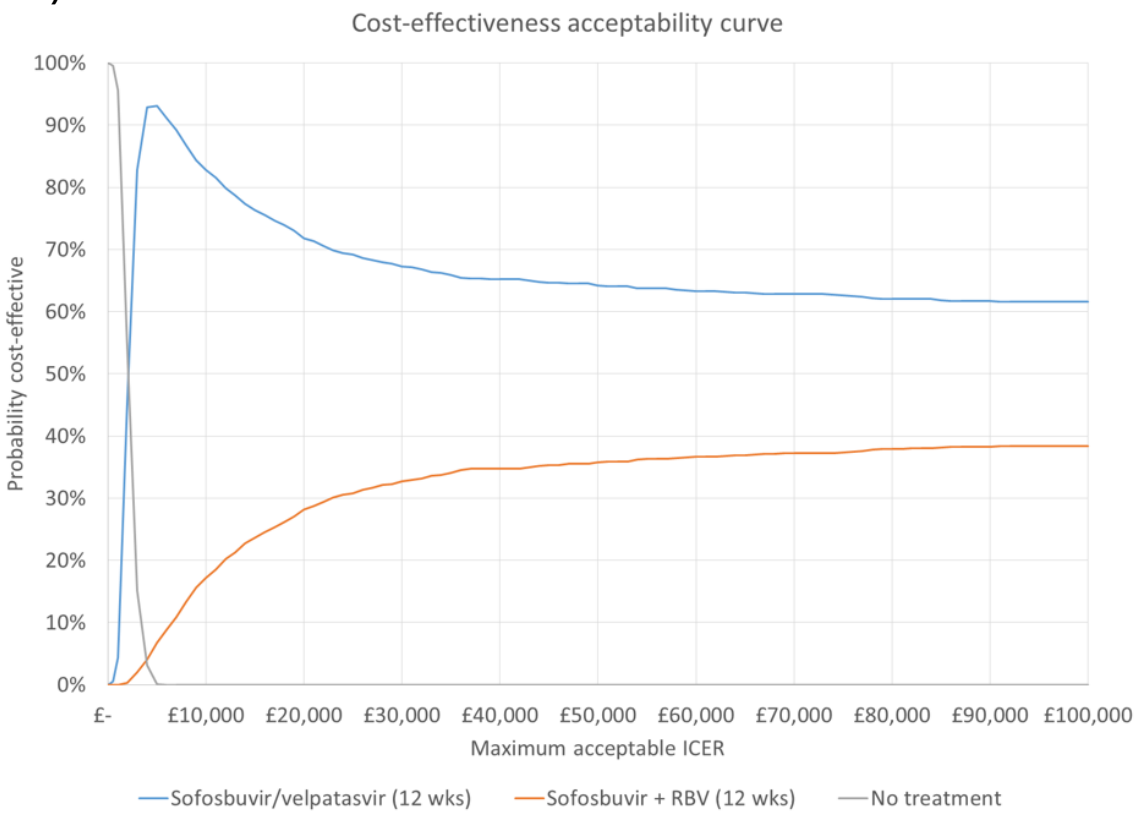
GT2 IFN-ineligible

GT2 treatment-naïve non-cirrhotic IFN-ineligible

Table 201: Probability of cost-effectiveness: GT2 treatment-naïve non-cirrhotic IFN-ineligible (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	72
£30,000	67

Figure 42: Multiple CEACs: GT2 treatment-naïve non-cirrhotic IFN-ineligible (discounted price)

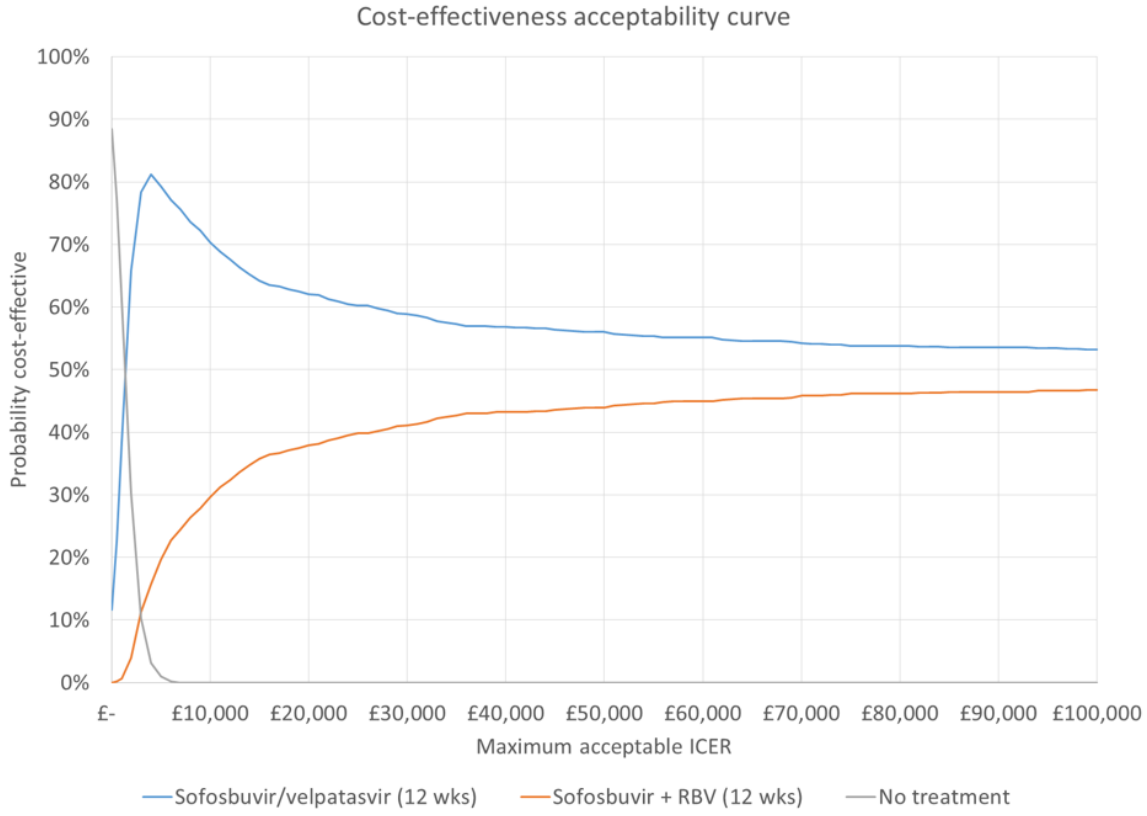


GT2 treatment-naïve cirrhotic IFN-ineligible

Table 202: Probability of cost-effectiveness: GT2 treatment-naïve cirrhotic IFN-ineligible (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	62
£30,000	59

Figure 43: Multiple CEACs: GT2 treatment-naïve cirrhotic IFN-ineligible (discounted price)

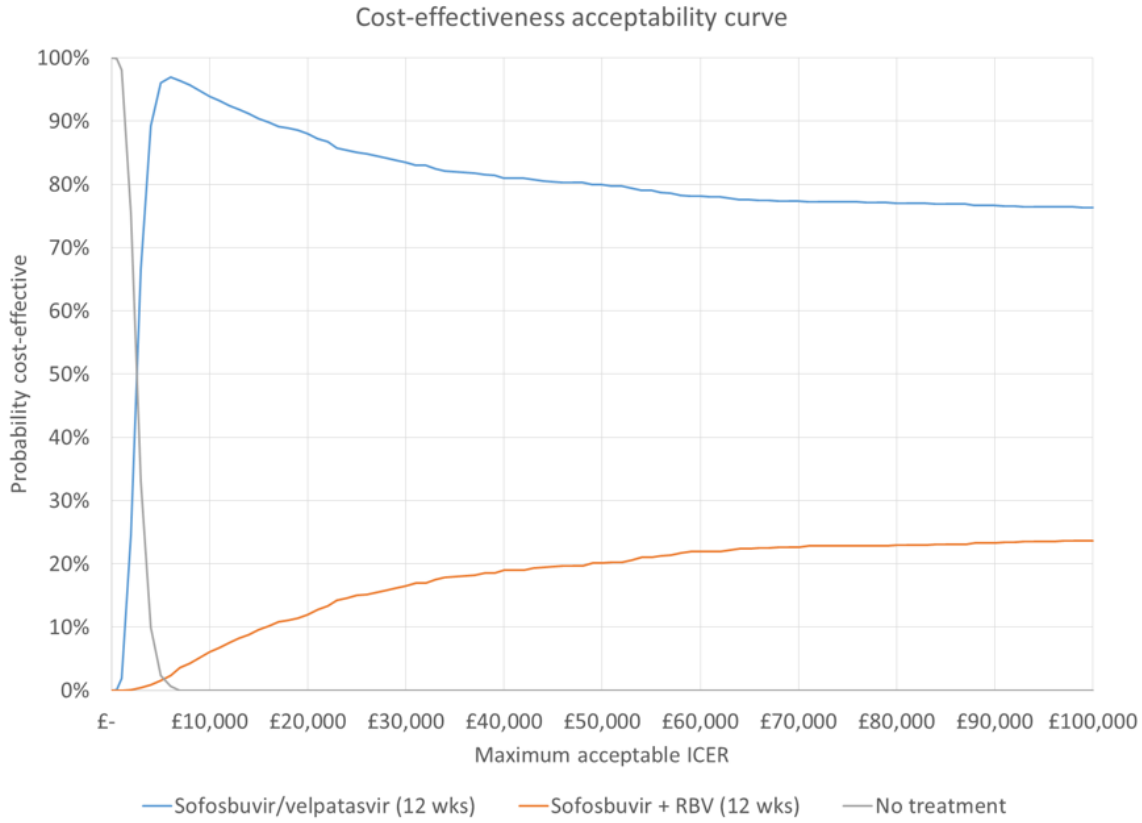


GT2 treatment-experienced non-cirrhotic IFN-ineligible

Table 203: Probability of cost-effectiveness: GT2 treatment-experienced non-cirrhotic IFN-ineligible (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	88
£30,000	84

Figure 44: Multiple CEACs: GT2 treatment-experienced non-cirrhotic IFN-ineligible (discounted price)

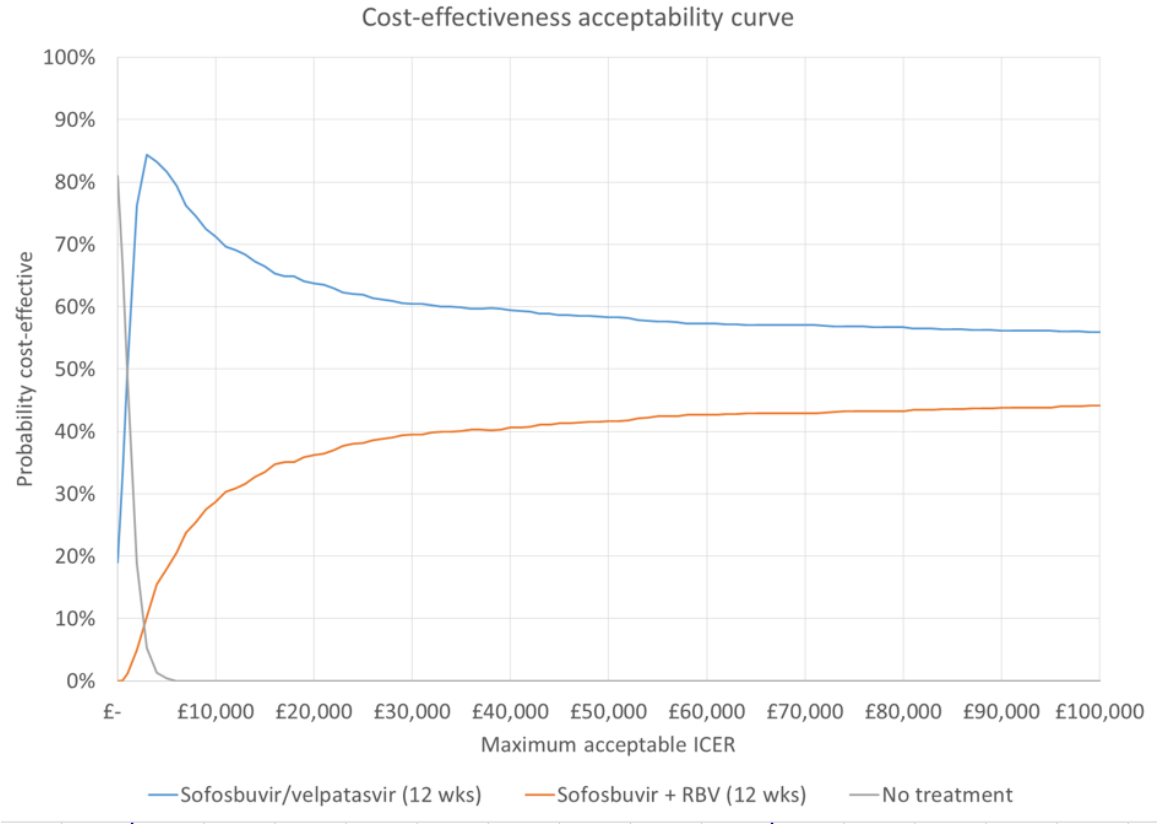


GT2 treatment-experienced cirrhotic IFN-ineligible

Table 204: Probability of cost-effectiveness: GT2 treatment-experienced cirrhotic IFN-ineligible (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	64
£30,000	61

Figure 45: Multiple CEACs: GT2 treatment-experienced cirrhotic IFN-ineligible (discounted price)



GT4 overall

GT4 treatment-naïve non-cirrhotic

Table 205: Probability of cost-effectiveness: GT4 treatment-naïve non-cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	41
£30,000	48

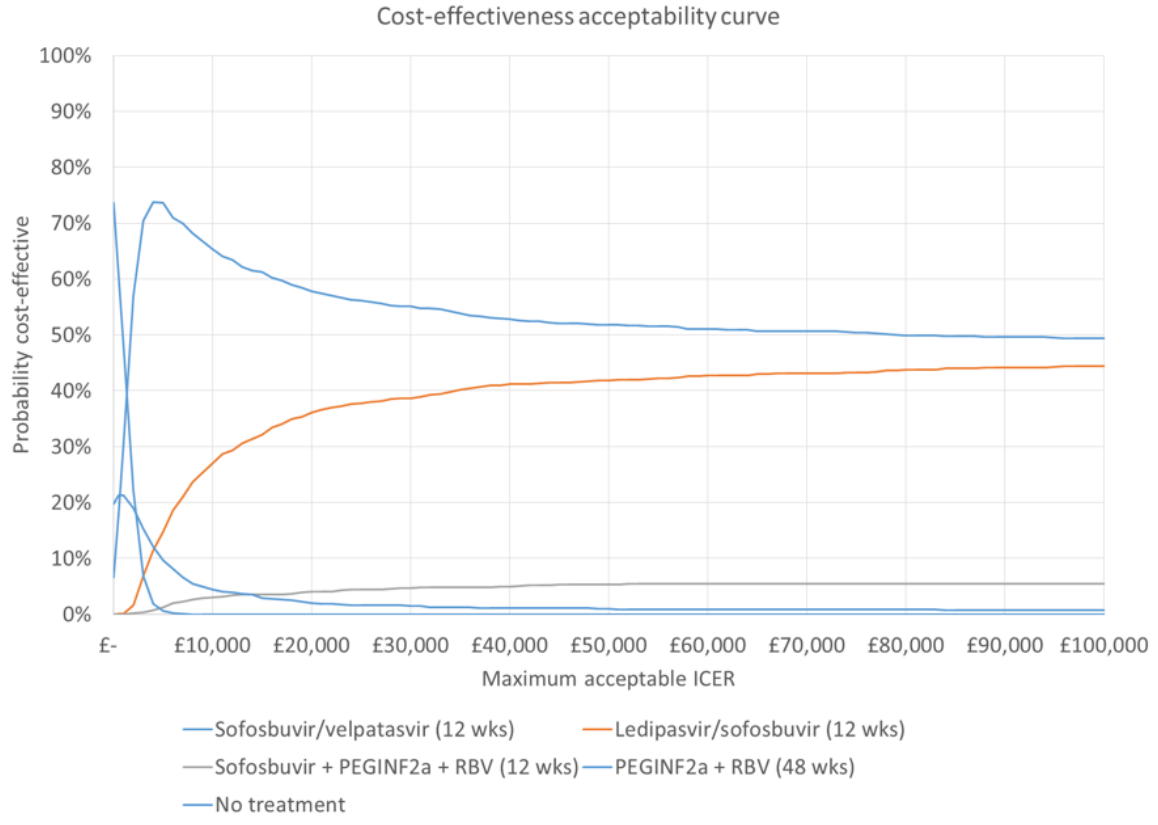
Figure 46: Multiple CEACs: GT4 treatment-naïve non-cirrhotic (anticipated list price)

GT4 treatment-naïve cirrhotic

Table 206: Probability of cost-effectiveness: GT4 treatment-naïve cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	58
£30,000	55

Figure 47: Multiple CEACs: GT4 treatment-naïve cirrhotic (discounted price)

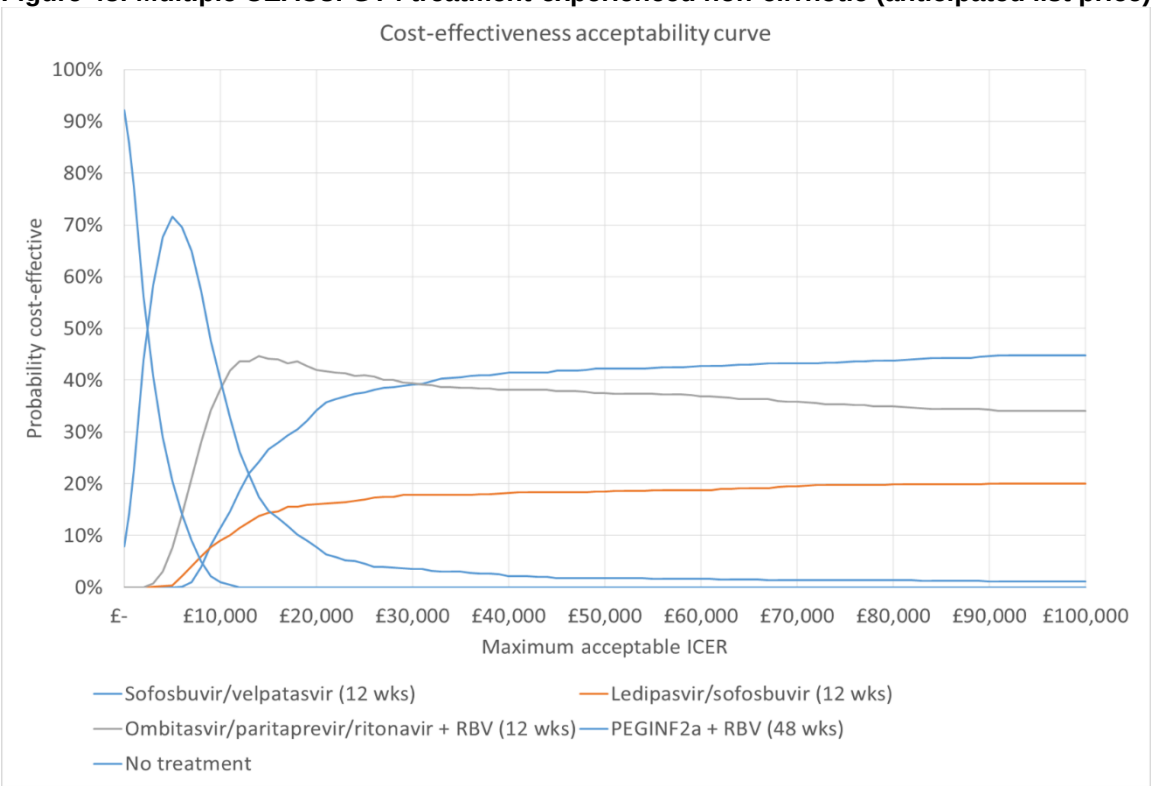


GT4 treatment-experienced non-cirrhotic

Table 207: Probability of cost-effectiveness: GT4 treatment-experienced non-cirrhotic (anticipated list price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	34
£30,000	39

Figure 48: Multiple CEACs: GT4 treatment-experienced non-cirrhotic (anticipated list price)

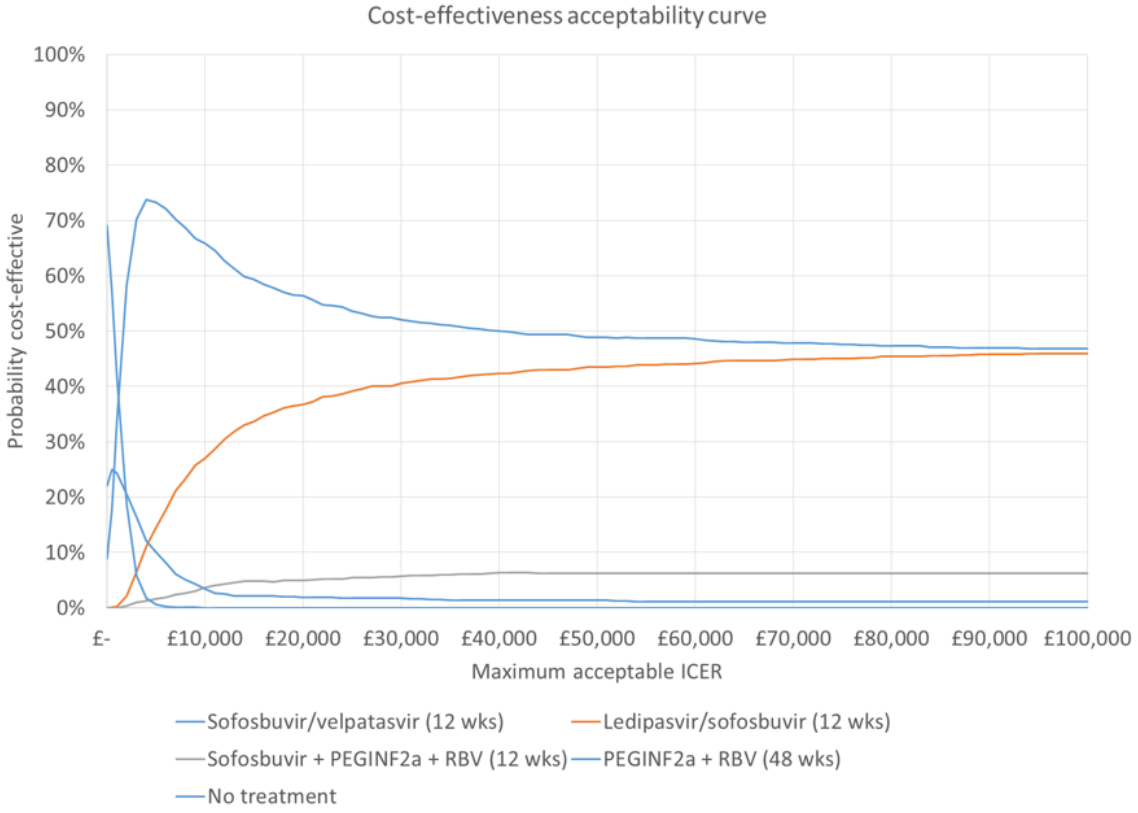


GT4 treatment-experienced cirrhotic

Table 208: Probability of cost-effectiveness: GT4 treatment-experienced cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	56
£30,000	52

Figure 49: Multiple CEACs: GT4 treatment-experienced cirrhotic (discounted price)



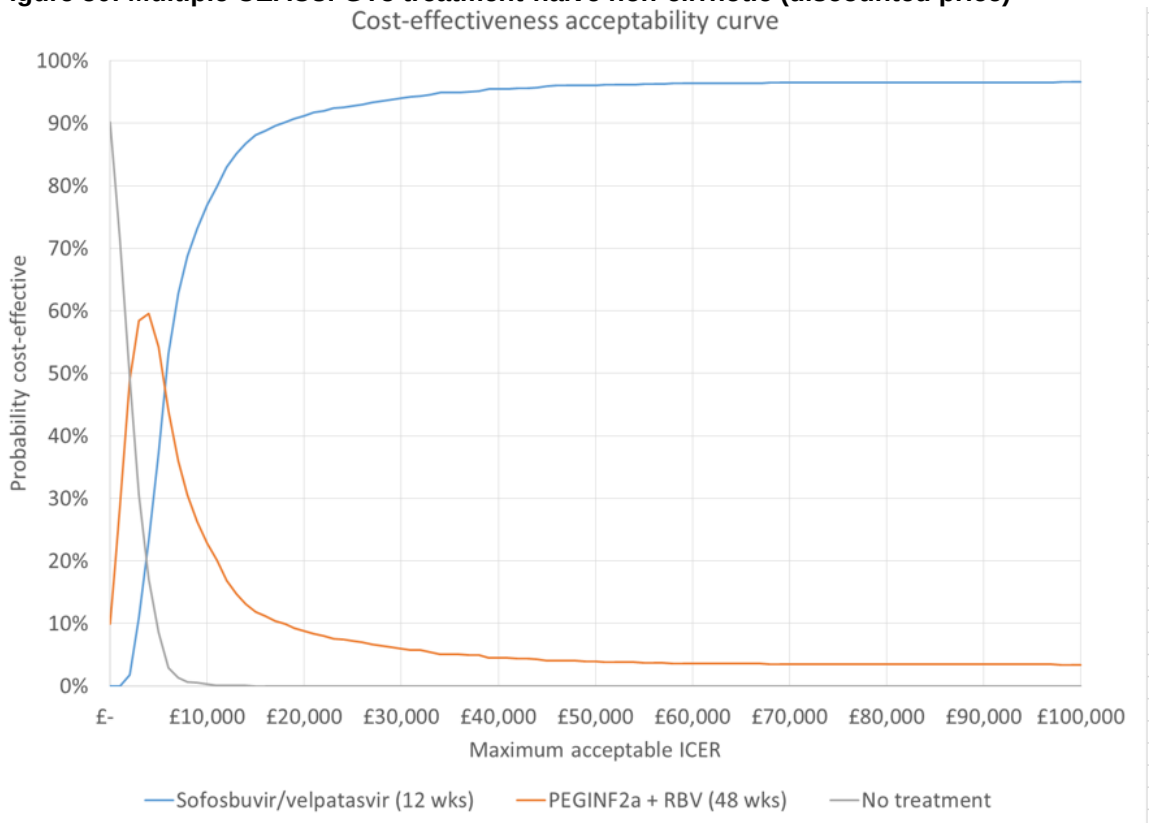
GT5 overall

GT5 treatment-naïve non-cirrhotic

Table 209: Probability of cost-effectiveness: GT5 treatment-naïve non-cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	91
£30,000	94

Figure 50: Multiple CEACs: GT5 treatment-naïve non-cirrhotic (discounted price)



GT5 treatment-naïve cirrhotic

Table 210: Probability of cost-effectiveness: GT5 treatment-naïve cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	91
£30,000	90

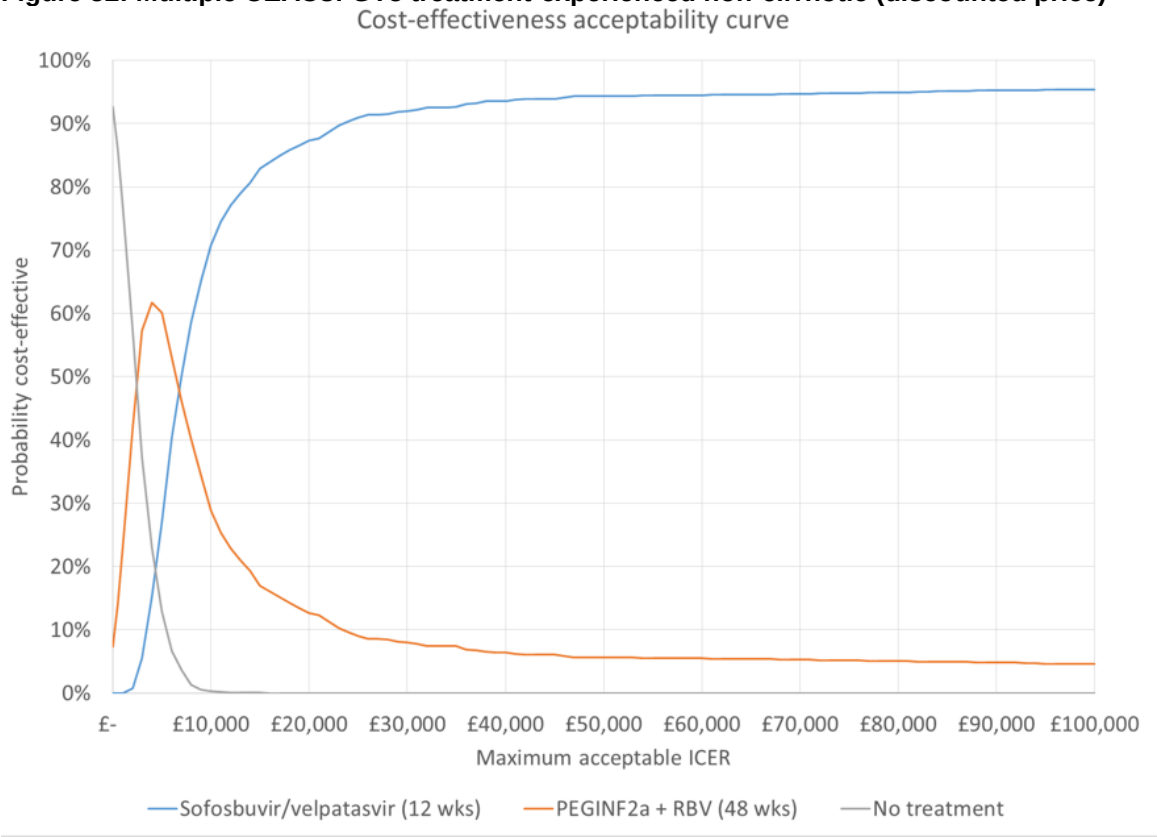
Figure 51: Multiple CEACs: GT5 treatment-naïve cirrhotic (discounted price)

GT5 treatment-experienced non-cirrhotic

Table 211: Probability of cost-effectiveness: GT5 treatment-experienced non-cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	87
£30,000	92

Figure 52: Multiple CEACs: GT5 treatment-experienced non-cirrhotic (discounted price)



GT5 treatment-experienced cirrhotic

Table 212: Probability of cost-effectiveness: GT5 treatment-experienced cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	89
£30,000	88

Figure 53: Multiple CEACs: GT5 treatment-experienced cirrhotic (discounted price)

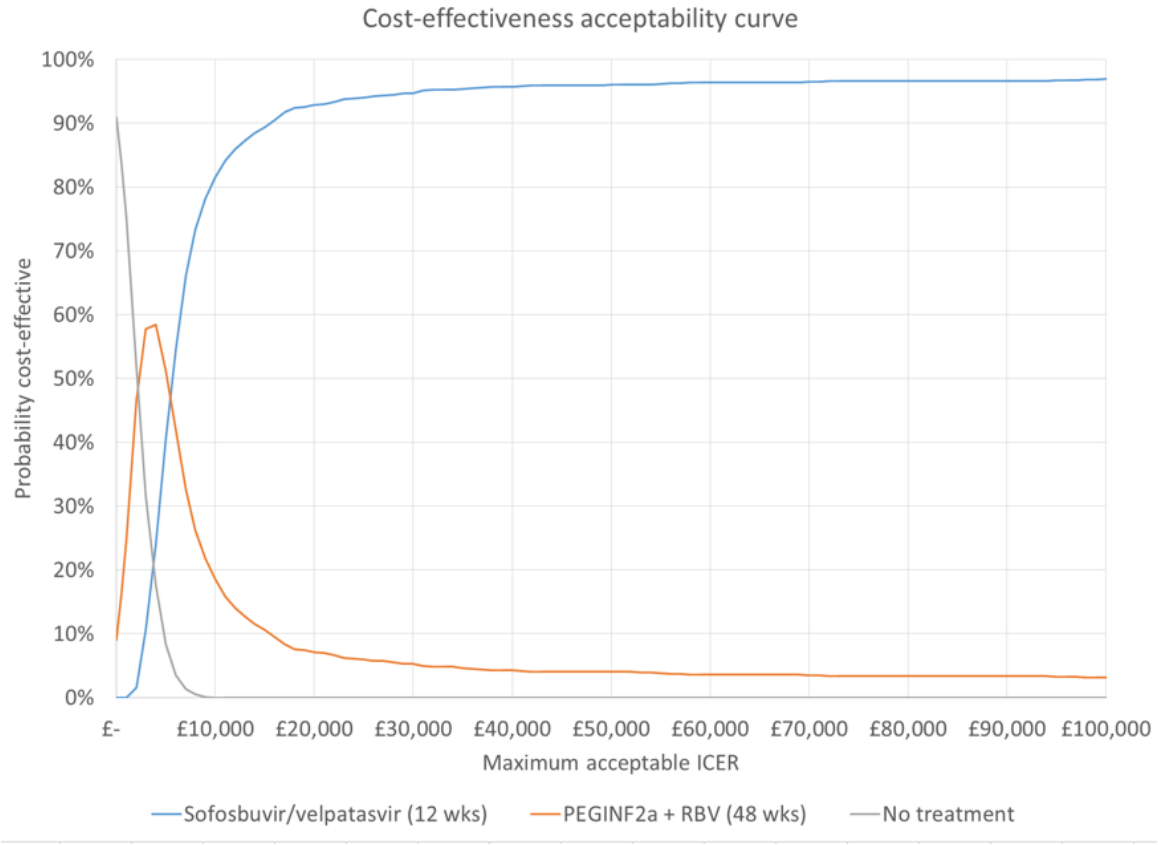
GT6 overall

GT6 treatment-naïve non-cirrhotic

Table 213: Probability of cost-effectiveness: GT6 treatment-naïve non-cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	93
£30,000	95

Figure 54: Multiple CEACs: GT6 treatment-naïve non-cirrhotic (discounted price)

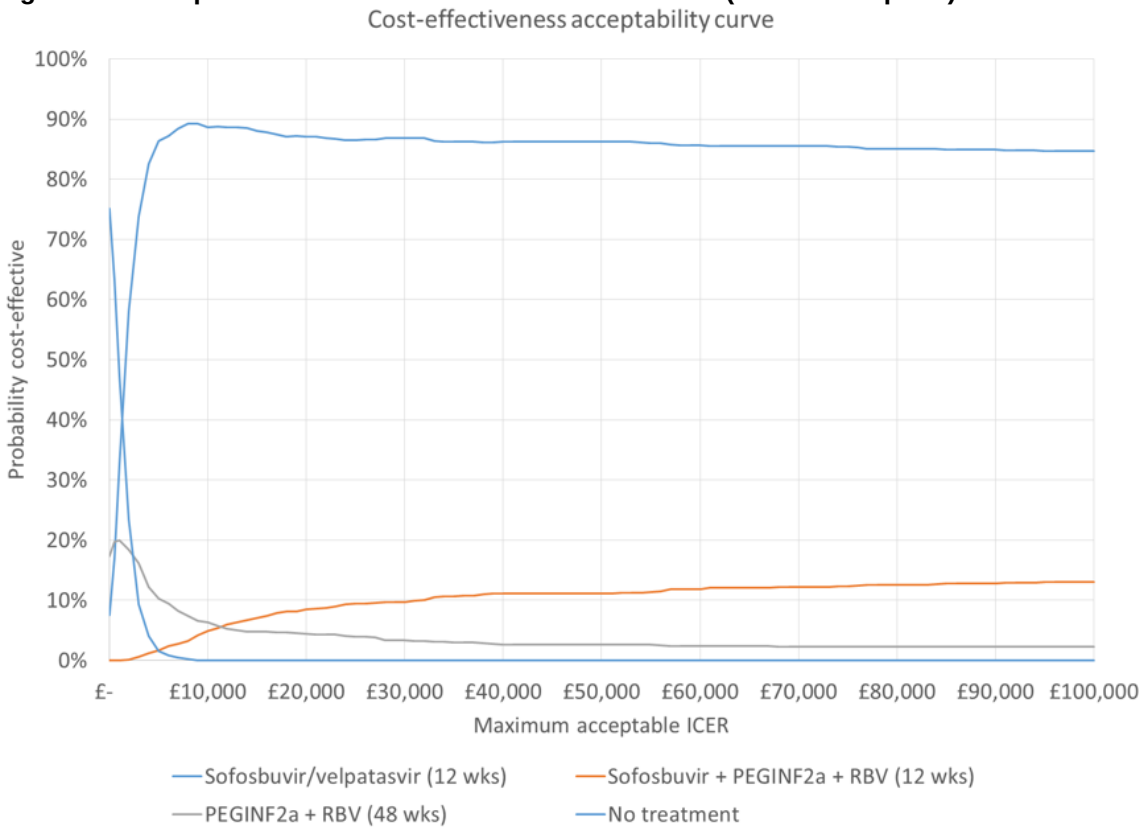


GT6 treatment-naïve cirrhotic

Table 214: Probability of cost-effectiveness: GT6 treatment-naïve cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	87
£30,000	87

Figure 55: Multiple CEACs: GT6 treatment-naïve cirrhotic (discounted price)

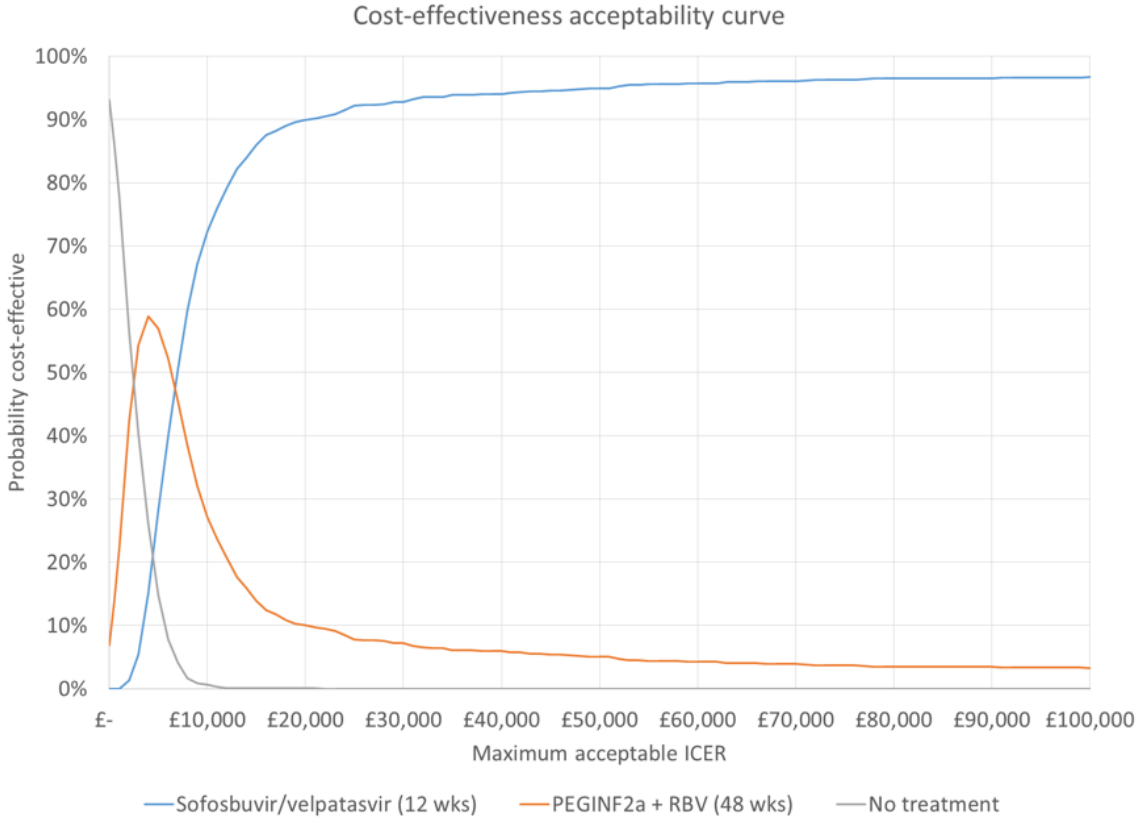


GT6 treatment-experienced non-cirrhotic

Table 215: Probability of cost-effectiveness: GT6 treatment-experienced non-cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	90
£30,000	93

Figure 56: Multiple CEACs: GT6 treatment-experienced non-cirrhotic (discounted price)

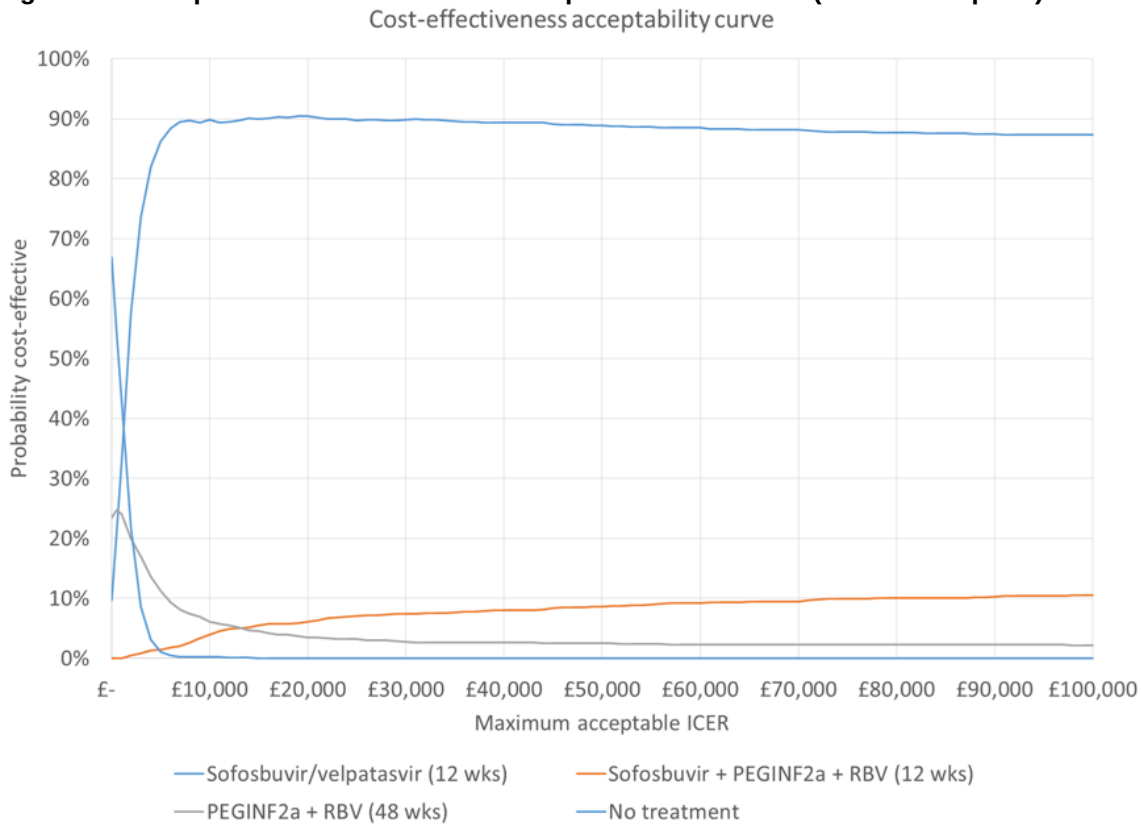


GT6 treatment-experienced cirrhotic

Table 216: Probability of cost-effectiveness: GT6 treatment-experienced cirrhotic (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	90
£30,000	90

Figure 57: Multiple CEACs: GT6 treatment-experienced cirrhotic (discounted price)



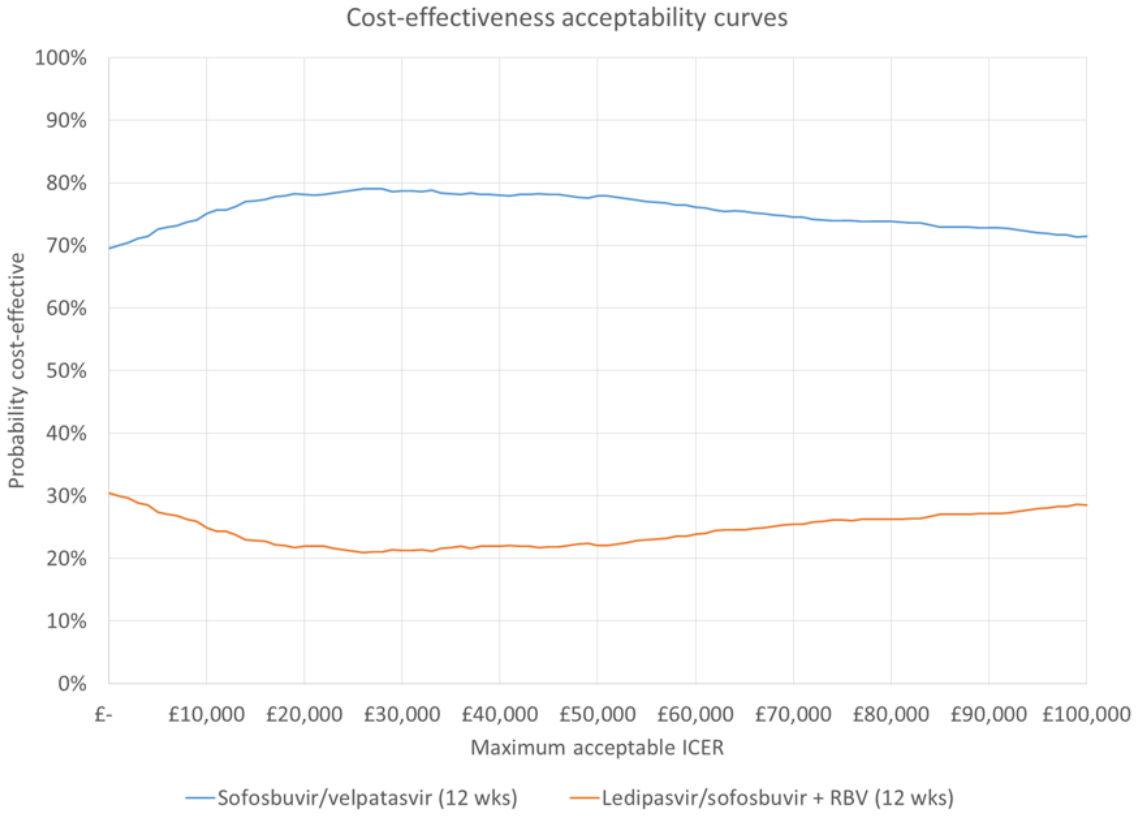
Decompensated cirrhosis

DCC treatment-naïve

Table 217: Probability of cost-effectiveness: DCC treatment-naïve (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	78
£30,000	79

Figure 58: Multiple CEACs: DCC treatment-naïve (discounted price)



DCC treatment-experienced

Table 218: Probability of cost-effectiveness: DCC treatment-experienced (discounted price)

Cost-effectiveness threshold	Probability of cost-effectiveness (%)
£20,000	77
£30,000	78

Figure 59: Multiple CEACs: DCC treatment-experienced (discounted price)

5.8.1.3 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 5.7).

For patients with CHC GT3, SOF/VEL is cost-effective compared to all comparators in treatment naïve and treatment experienced patients.

- The probability that SOF/VEL is the most cost-effective option at a threshold of £20,000 per QALY is 59% for GT3 treatment naïve non cirrhotic patients
- The probability that SOF/VEL is the most cost-effective option at a threshold of £20,000 per QALY is 63% for GT3 treatment naïve cirrhotic patients
- The probability that SOF/VEL is the most cost-effective option at a threshold of £20,000 per QALY is 64% for GT3 treatment experienced non cirrhotic patients
- The probability that SOF/VEL is the most cost-effective option at a threshold of £20,000 per QALY is 65% for GT3 treatment experienced cirrhotic patients

In GT3 IFN-ineligible patients the probability that SOF/VEL is the most cost-effective option at a threshold of £20,000 per QALY is ≥85% in all GT3 IFN-ineligible indications.

In GT1 patients the probability of SOF/VEL being cost-effective ranged from 14–53% at a threshold of £20,000 per QALY. It should be noted that this analysis was perfomed using the anticipated list price for SOF/VEL and is therefore not truly reflective of the cost-effectiveness of SOF/VEL.

In GT2 patients who are treatment naïve, SOF/VEL has the highest probability of being cost effective at a threshold of £30,000 per QALY.

In GT2 patients who are treatment experienced, SOF/VEL has the highest probability of being cost effective at a threshold of £20,000 per QALY compared to all comparators in all indications. This is also the case in all GT2 indications when patients are IFN-ineligible.

In GT5 and GT6 patients, SOF/VEL has the highest probability (>85%) of being cost effective at a threshold of £20,000 per QALY compared to all comparators in all indications.

In DCC patients, SOF/VEL has a probability of over 70% of being cost-effective at a threshold of £20,000 per QALY compared to LDV/SOF+RBV (12w).

5.8.2 *Deterministic sensitivity analysis*

5.8.2.1 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 219 below.

Table 219: Generic DSA input values

Parameter	Base-case	Min	Max	Source
Health state costs				
Non-cirrhotic disease – No treatment	£327	£245	£409	Assumption: +/- 25% of the base-case
Cirrhotic disease – No treatment – Pharmacy	£390	£293	£488	Assumption: +/- 25% of the base-case
Cirrhotic disease – No treatment –	£390	£293	£488	Assumption: +/- 25% of

Parameter	Base-case	Min	Max	Source
Hospitalisation				the base-case
Cirrhotic disease – No treatment – Outpatient	£780	£585	£976	Assumption: +/- 25% of the base-case
Cirrhotic disease – No treatment – Emergency	£390	£293	£488	Assumption: +/- 25% of the base-case
Cirrhotic disease – No treatment – Ambulatory	£390	£293	£488	Assumption: +/- 25% of the base-case
Decompensated cirrhosis - Pharmacy	£3,127	£2,346	£3,909	Assumption: +/- 25% of the base-case
Decompensated cirrhosis – Hospitalisation	£3,127	£2,346	£3,909	Assumption: +/- 25% of the base-case
Decompensated cirrhosis – Outpatient	£6,255	£4,691	£7,819	Assumption: +/- 25% of the base-case
Decompensated cirrhosis – Emergency	£3,127	£2,346	£3,909	Assumption: +/- 25% of the base-case
Decompensated cirrhosis – Ambulatory	£3,127	£2,346	£3,909	Assumption: +/- 25% of the base-case
Non-cirrhotic disease – SVR	£246	£184	£307	Assumption: +/- 25% of the base-case
Cirrhotic disease – SVR - Pharmacy	£128	£96	£160	Assumption: +/- 25% of the base-case
Cirrhotic disease – SVR – Hospitalisation	£128	£96	£160	Assumption: +/- 25% of the base-case
Cirrhotic disease – SVR – Outpatient	£256	£192	£320	Assumption: +/- 25% of the base-case
Cirrhotic disease – SVR – Emergency	£128	£96	£160	Assumption: +/- 25% of the base-case
Cirrhotic disease – SVR – Ambulatory	£128	£96	£160	Assumption: +/- 25% of the base-case
Decompensated cirrhosis - SVR - Pharmacy	£3,127	£2,346	£3,909	Assumption: +/- 25% of the base-case
Decompensated cirrhosis - SVR - Hospitalisation	£3,127	£2,346	£3,909	Assumption: +/- 25% of the base-case
Decompensated cirrhosis - SVR - Outpatient	£6,255	£4,691	£7,819	Assumption: +/- 25% of the base-case
Decompensated cirrhosis - SVR - Emergency	£3,127	£2,346	£3,909	Assumption: +/- 25% of the base-case
Decompensated cirrhosis - SVR - Ambulatory	£3,127	£2,346	£3,909	Assumption: +/- 25% of the base-case
Hepatocellular carcinoma - Pharmacy	£2,787	£2,090	£3,483	Assumption: +/- 25% of the base-case
Hepatocellular carcinoma – Hospitalisation	£2,787	£2,090	£3,483	Assumption: +/- 25% of the base-case
Hepatocellular carcinoma – Outpatient	£5,573	£4,180	£6,967	Assumption: +/- 25% of the base-case
Hepatocellular carcinoma – Emergency	£2,787	£2,090	£3,483	Assumption: +/- 25% of the base-case

Parameter	Base-case	Min	Max	Source
Hepatocellular carcinoma – Ambulatory	£2,787	£2,090	£3,483	Assumption: +/- 25% of the base-case
Liver transplant - Pharmacy	£21,298	£15,973	£26,622	Assumption: +/- 25% of the base-case
Liver transplant – Hospitalisation	£21,298	£15,973	£26,622	Assumption: +/- 25% of the base-case
Liver transplant – Outpatient	£42,595	£31,947	£53,244	Assumption: +/- 25% of the base-case
Liver transplant – Emergency	£21,298	£15,973	£26,622	Assumption: +/- 25% of the base-case
Liver transplant – Ambulatory	£21,298	£15,973	£26,622	Assumption: +/- 25% of the base-case
Post-liver transplant – Year 1	£28,067	£21,051	£35,084	Assumption: +/- 25% of the base-case
Post-liver transplant – Year 2	£4,194	£3,145	£5,242	Assumption: +/- 25% of the base-case
Utility weights				
Non-cirrhotic	0.751	0.601	0.902	Assumption: +/- 20% of the base-case
Cirrhotic	0.550	0.440	0.660	Assumption: +/- 20% of the base-case
Decompensated cirrhosis	0.450	0.360	0.540	Assumption: +/- 20% of the base-case
SVR - Utility increment	0.040	0.032	0.048	Assumption: +/- 20% of the base-case
Hepatocellular carcinoma	0.450	0.360	0.540	Assumption: +/- 20% of the base-case
Liver transplant	0.450	0.360	0.540	Assumption: +/- 20% of the base-case
Post-liver transplant	0.670	0.536	0.804	Assumption: +/- 20% of the base-case
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	0.014	0.002	0.039	Based on the PSA

Parameter	Base-case	Min	Max	Source
to HCC				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	Based on the PSA distribution
From decompensated cirrhotic SVR to decompensated cirrhotic (re-infection)	0.000	0.000	0.100	Based on the PSA distribution
From HCC to liver transplant	0.000	0.000	0.100	Based on the PSA distribution
Discounting				
Outcomes	3.5%	0.0%	6.0%	NICE guidelines
Costs	3.5%	0.0%	6.0%	NICE guidelines

DSA, Deterministic sensitivity analysis; HCC, Hepatocellular carcinoma; NICE, National Institute of Health and Excellence; PSA, Probabilistic sensitivity analysis; SVR, Sustained virologic response

Indication-specific DSA inputs

In addition to the generic inputs listed above in Table 219, 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 sofosbuvir, and for LDV/SOF. 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, 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 220: Indication-specific DSA input values

Variables	Method to estimate lower and upper inputs for the DSA
Treatment-specific SVR	95% CI estimated from the PSA
Treatment-specific AE rates	Between 0% and 25%

Variables	Method to estimate lower and upper inputs for the DSA
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

5.8.2.2 Results

Selected treatment comparisons in selected populations have been presented.

GT3 treatment-naïve non-cirrhotic

In this comparison, the ICER was most sensitive to the discount rate (varied between 0% and 6%), and the treatment costs for SOF/VEL 12 weeks, and the SVR rate for Peg-IFN+RBV 24 weeks.

The base-case ICER is £15,199 per QALY gained for SOF/VEL vs Peg-IFN+RBV 24 weeks. Across all parameters varied in this DSA, the ICER for SOF-VEL versus Peg-IFN+RBV 24 weeks did not exceed £30,000 per QALY.

Figure 60: Tornado diagram (GT3 TN NC: SOF/VEL 12 weeks vs Peg-IFN+RBV 24 weeks) (discounted price)

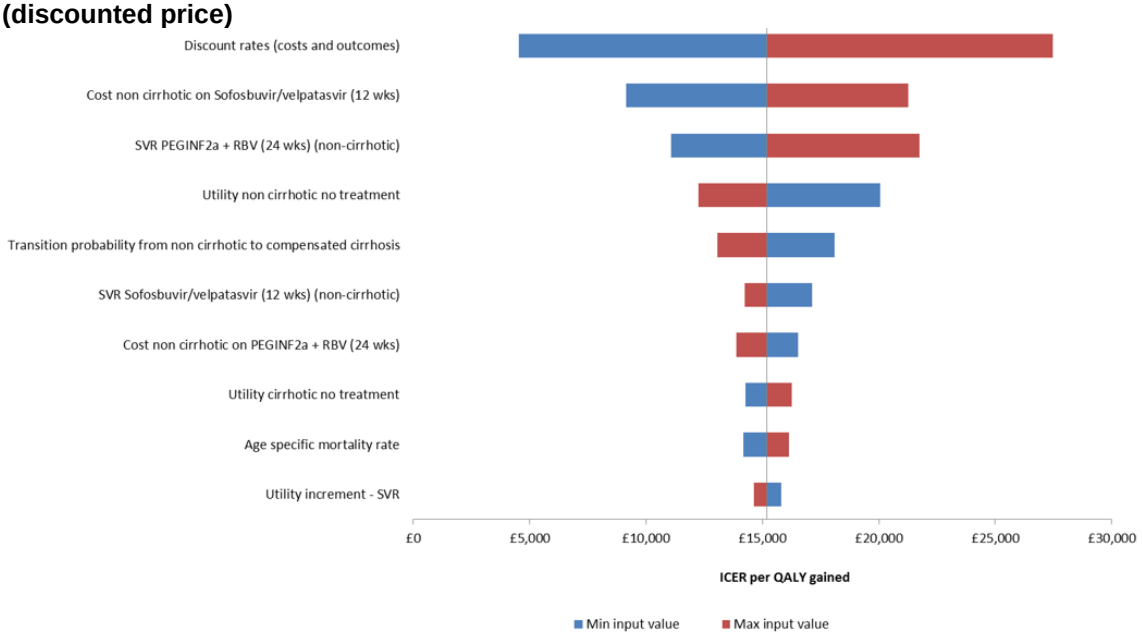


Table 221: Input values and ICERs for DSA (GT3 TN NC: SOF/VEL 12 weeks vs Peg-IFN+RBV 24 weeks (discounted price)

Parameter	Value			ICER, cost/QALY		
	Base-case	Min.	Max.	Min.	Max.	Diff.
Discount rates (costs and outcomes)	3.5%	0.0%	6.0%	£4,517	£27,471	£22,954
Cost non cirrhotic on Sofosbuvir/velpatasvir (12 wks)	[redacted]	[redacted]	[redacted]	£9,131	£21,267	£12,137
SVR Peg-IFN+RBV (24	0.71	0.63	0.78	£11,063	£21,735	£10,672

Parameter	Value			ICER, cost/QALY		
	Base-case	Min.	Max.	Min.	Max.	Diff.
wks) (non-cirrhotic)						
Utility non cirrhotic no treatment	0.75	0.60	0.90	£20,056	£12,236	£7,821
Transition probability from non-cirrhotic to compensated cirrhosis	0.030	0.028	0.031	£18,103	£13,052	£5,052
SVR Sofosbuvir/velpatasvir (12 wks) (non-cirrhotic)	0.98	0.96	1.00	£17,120	£14,249	£2,871
Cost non cirrhotic on Peg-IFN+RBV (24 wks)	£6,605	£4,954	£8,257	£16,523	£13,875	£2,648
Utility cirrhotic no treatment	0.55	0.44	0.66	£14,277	£16,248	£1,971
Age specific mortality rate	Age specific	-25%	+25%	£14,183	£16,128	£1,945
Utility increment - SVR	0.04	0.032	0.048	£15,798	£14,644	£1,154

Diff., difference; ICER, incremental cost-effectiveness ratio; Min., minimum; Max., maximum; Peg-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; SVR, sustained virologic response.

GT1 treatment-naïve non-cirrhotic

In this comparison, the ICER was most sensitive to the SVR rate for LDV/SOF 8 weeks, the treatment cost for SOF/VEL, and the treatment cost for LDV/SOF 8 weeks.

The base-case ICER is £8,555 per QALY gained for SOF/VEL vs LDV/SOF 8 weeks. SOF/VEL is a dominant strategy if the minimum SOF/VEL treatment cost is used, and all other parameters held the same. SOF/VEL is also a dominant strategy if the maximum LDV/SOF 8 weeks treatment cost is applied.

Figure 61: Tornado diagram (GT1 TN NC: SOF/VEL 12 weeks vs LDV/SOF 8 weeks) (discounted price)

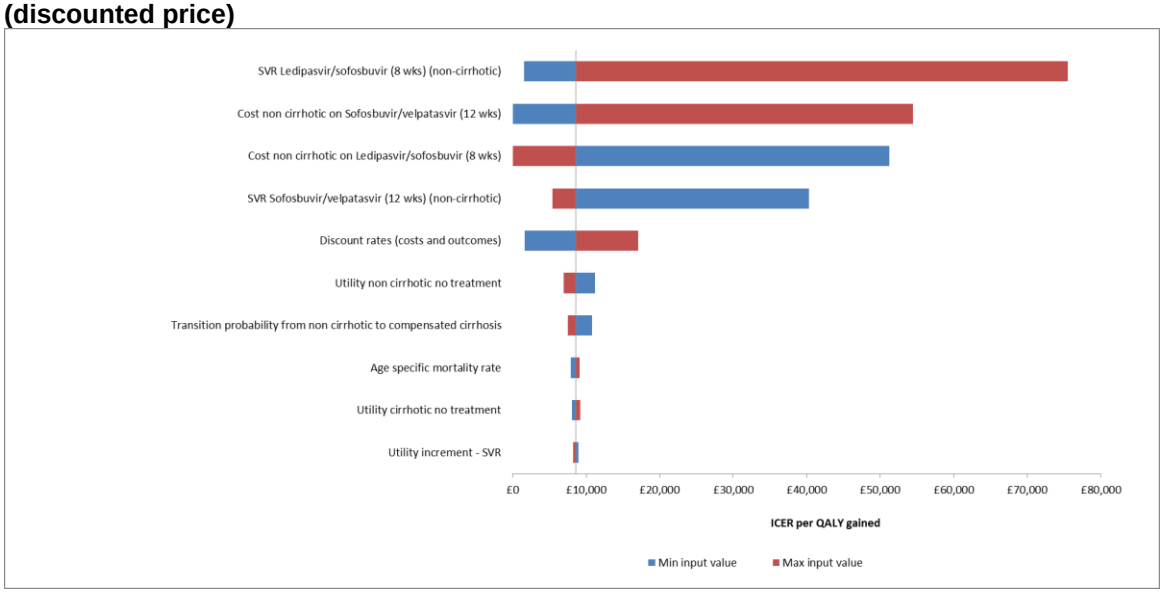


Table 222: Input values and ICERs for DSA (GT1 TN NC: SOF/VEL 12 weeks vs LDV/SOF 8 weeks) (discounted price)

Parameter	Value			ICER, cost/QALY		
	Base-case	Min.	Max.	Min.	Max.	Diff.
SVR Ledipasvir/sofosbuvir (8 wks) (non-cirrhotic)	0.94	0.89	0.98	£1,571	£75,523	£73,952
Cost non cirrhotic on Sofosbuvir/velpatasvir (12 wks)	[redacted]	[redacted]	[redacted]	SOF/VEL dominates	£54,427	£45,871
Cost non cirrhotic on Ledipasvir/sofosbuvir (8 wks)	£28,086	£21,064	£35,107	£51,212	SOF/VEL dominates	£42,657
SVR Sofosbuvir/velpatasvir (12 wks) (non-cirrhotic)	0.98	0.95	1.00	£40,332	£5,405	£34,927
Discount rates (costs and outcomes)	3.5%	0.0%	6.0%	£1,633	£17,080	£15,447
Utility non cirrhotic no treatment	0.75	0.60	0.90	£11,226	£6,911	£4,315
Transition probability from non-cirrhotic to compensated cirrhosis	0.0213	0.0159	0.0249	£10,767	£7,503	£3,265
Age specific mortality rate	Age specific	-25%	+25%	£7,922	£9,131	£1,209
Utility cirrhotic no treatment	0.55	0.44	0.66	£8,034	£9,149	£1,114
Utility increment - SVR	0.04	0.03	0.05	£8,935	£8,207	£728

Diff., difference; ICER, incremental cost-effectiveness ratio; Min., minimum; Max., maximum; Peg-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

GT2 treatment-naïve non-cirrhotic

In this comparison, the ICER was most sensitive to the discount rate (varied between 0% and 6%), the SVR for Peg-IFN+RBV 24 weeks, and the treatment cost for SOF/VEL.

The base-case ICER is £32,595 per QALY gained for SOF/VEL versus Peg-IFN+RBV 24 weeks.

Figure 62: Tornado diagram (GT2 TN NC: SOF/VEL 12 weeks vs Peg-IFN+RBV 24 weeks) (discounted price)

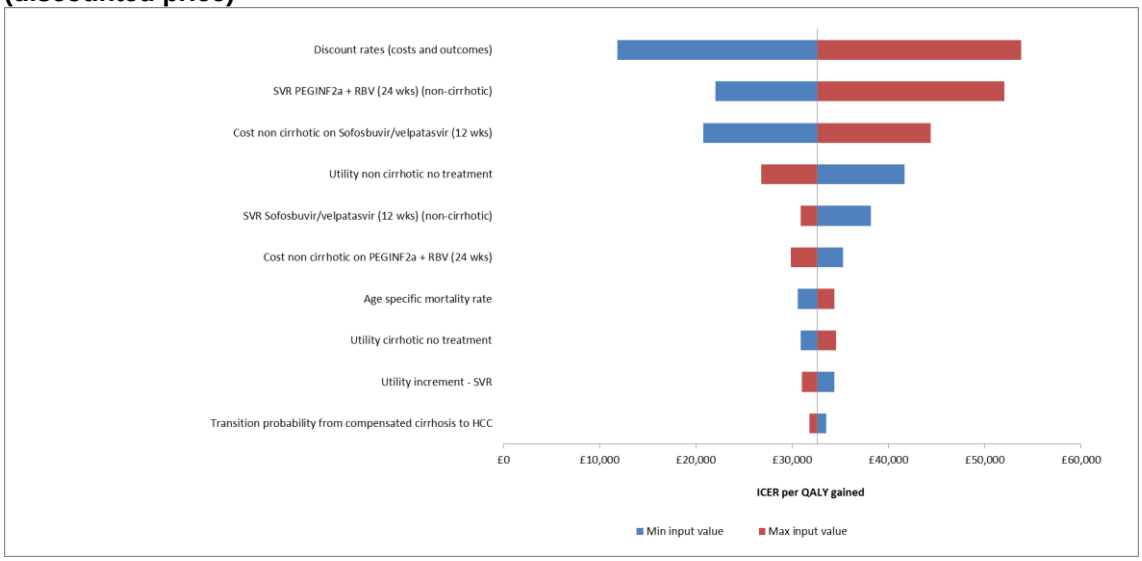


Table 223: Input values and ICERs for DSA (GT2 TN NC: SOF/VEL 12 weeks vs Peg-IFN+RBV 24 weeks) (discounted price)

Parameter	Value			ICER, cost/QALY		
	Base-case	Min.	Max.	Min.	Max.	Diff.
Discount rates (costs and outcomes)	3.5%	0.0%	6.0%	£11,852	£53,796	£41,944
SVR Peg-IFN+RBV (24 wks) (non-cirrhotic)	0.81	0.72	0.88	£22,002	£52,054	£30,052
Cost non cirrhotic on Sofosbuvir/velpatasvir (12 wks)	[redacted]	[redacted]	[redacted]	£20,772	£44,419	£23,647
Utility non cirrhotic no treatment	0.75	0.60	0.90	£41,659	£26,771	£14,888
SVR Sofosbuvir/velpatasvir (12 wks) (non-cirrhotic)	0.99	0.96	1.00	£38,165	£30,902	£7,263
Cost non cirrhotic on Peg-IFN+RBV (24 wks)	£6,885	£5,163	£8,606	£35,302	£29,889	£5,413
Age specific mortality rate	Age specific	-25%	+25%	£30,587	£34,412	£3,825

Parameter	Value			ICER, cost/QALY		
	Base-case	Min.	Max.	Min.	Max.	Diff.
Utility cirrhotic no treatment	0.55	0.44	0.66	£30,860	£34,537	£3,677
Utility increment – SVR	0.04	0.03	0.05	£34,385	£30,983	£3,402
Transition probability from compensated cirrhosis to HCC	0.063	0.047	0.081	£33,514	£31,800	£1,714

Diff., difference; ICER, incremental cost-effectiveness ratio; Min., minimum; Max., maximum; Peg-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; SVR, sustained virologic response.

GT4 treatment-naïve non-cirrhotic

In this comparison, the ICER was most sensitive to the discount rate (varied between 0% and 6%), the treatment cost for SOF/VEL, and the SVR rate for Peg-IFN+RBV 48 weeks.

The base-case ICER is £5,212 per QALY for SOF/VEL versus Peg-IFN+RBV 48 weeks. When applying any minimum or maximum parameter value in the DSA, the ICER for SOF/VEL versus Peg-IFN+RBV 48 weeks was found to be consistently below £11,000 per QALY.

Figure 63: Tornado diagram (GT4 TN NC: SOF/VEL 12 weeks vs Peg-IFN+RBV 48 weeks) (discounted price)

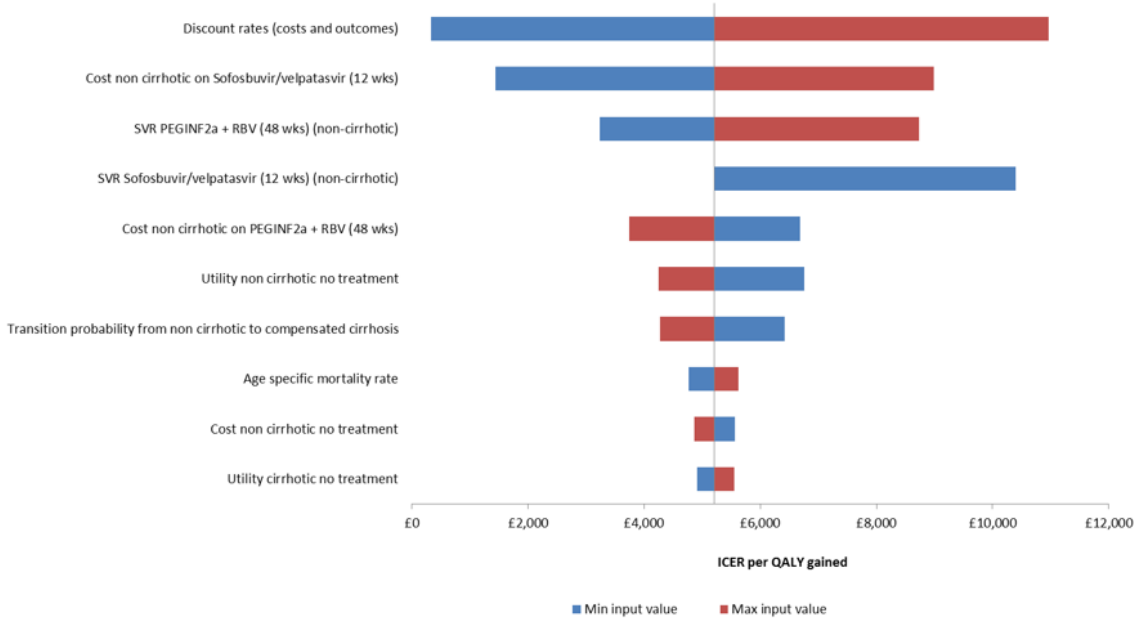


Table 224: Input values and ICERs for DSA (GT4 TN NC: SOF/VEL 12 weeks vs Peg-IFN+RBV 48 weeks) (discounted price)

Parameter	Value			ICER, cost/QALY		
	Base-case	Min.	Max.	Min.	Max.	Diff.
Discount rates (costs and outcomes)	3.5%	0.0%	6.0%	£325	£10,970	£10,646
Cost non cirrhotic on	[redacted]	[redacted]	[redacted]	£1,433	£8,991	£7,558

Parameter	Value			ICER, cost/QALY		
	Base-case	Min.	Max.	Min.	Max.	Diff.
Sofosbuvir/velpatasvir (12 wks)						
SVR Peg-IFN+RBV (48 wks) (non-cirrhotic)	0.45	0.29	0.61	£3,239	£8,734	£5,495
SVR Sofosbuvir/velpatasvir (12 wks) (non-cirrhotic)	1.00	0.80	1.00	£10,398	£5,212	£5,186
Cost non cirrhotic on Peg-IFN+RBV (48 wks)	£11,785	£8,839	£14,732	£6,683	£3,741	£2,942
Utility non cirrhotic no treatment	0.75	0.60	0.90	£6,755	£4,243	£2,512
Transition probability from non-cirrhotic to compensated cirrhosis	0.020	0.017	0.024	£6,419	£4,269	£2,149
Age specific mortality rate	Age specific	-25%	+25%	£4,767	£5,623	£856
Cost non cirrhotic no treatment	£327	£245	£409	£5,563	£4,861	£702
Utility cirrhotic no treatment	0.55	0.44	0.66	£4,908	£5,556	£648

Diff., difference; ICER, incremental cost-effectiveness ratio; Min., minimum; Max., maximum; Peg-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; SVR, sustained virologic response.

5.8.3 *Scenario analysis*

Scenario analyses were conducted to provide additional cost-effectiveness evidence. In particular, a small number of comparator treatments, in some patient populations, were not included in the base-case set of cost-effectiveness results. These treatments were not included in the base-case economic model, on the basis that their usage and relevance to current clinical practice in CHC is expected to be extremely low. Assumptions have therefore been required to enable the incorporation of these comparator treatments by way of scenario analysis. These assumptions are clearly reported with the results in the following sections.

5.8.3.1 GT1 IFN-ineligible

GT1a treatment-naïve cirrhotic IFN-ineligible

In this scenario SOF+DCV+RBV 24 weeks was included as an additional comparator. SVR data for SOF+DCV+RBV in GT1 treatment-naïve cirrhotic patients was used (see SVR Table 98), but it was assumed that all other data was equal to SOF+DCV+RBV 24 weeks in GT3 treatment-experienced cirrhotic patients.

Table 225: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
Sofosbuvir/velpatasvir (12 wks)	£59,242	17.45	10.18	£23,452	8.09	8.09	£4,510	£4,510
Ledipasvir/sofosbuvir (12 wks)	£60,349	16.98	9.88	£24,559	7.62	7.62	£5,012	Dominated
Sofosbuvir + daclatasvir + RBV (24 wks)	£81,230	15.92	9.23	£45,440	6.56	6.56	£10,692	Dominated
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	£92,126	16.96	9.84	£56,336	7.60	7.6	£11,592	£17,862

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1a treatment-experienced cirrhotic IFN-ineligible

In this scenario SOF+DCV+RBV 24 weeks was included as an additional comparator. SVR data for SOF+DCV+RBV in GT1 treatment-experienced cirrhotic patients was used (see SVR Table 105), but it was assumed that all other data was equal to SOF+DCV+RBV 24 weeks in GT3 treatment-experienced cirrhotic patients.

Table 226: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,361	9.27	4.93					
Sofosbuvir/velpatasvir (12 wks)	£57,610	16.76	9.78	£22,249	7.49	7.49	£4,587	£4,587
Ledipasvir/sofosbuvir (12 wks)	£60,288	15.75	9.12	£24,927	6.48	6.48	£5,949	Dominated
Sofosbuvir + daclatasvir + RBV (24 wks)	£79,824	16.52	9.61	£44,463	7.25	7.25	£9,501	£39,869
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (24 wks)	£90,077	16.50	9.58	£54,716	7.23	7.23	£11,767	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1b treatment-naïve cirrhotic IFN-ineligible

In this scenario SOF+DCV+RBV 24 weeks was included as an additional comparator. SVR data for SOF+DCV+RBV in GT1 treatment-naïve cirrhotic patients was used (see SVR Table 98), but it was assumed that all other data was equal to SOF+DCV+RBV 24 weeks in GT3 in GT3 treatment-experienced cirrhotic patients.

Table 227: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	£56,300	17.45	10.17	£20,510	8.09	8.09	£3,952	£3,952
Sofosbuvir/velpatasvir (12 wks)	£59,242	17.45	10.18	£23,452	8.09	8.09	£4,510	£294,200
Ledipasvir/sofosbuvir (12 wks)	£60,349	16.98	9.88	£24,559	7.62	7.62	£5,012	Dominated
Sofosbuvir + daclatasvir + RBV (24 wks)	£81,230	15.92	9.23	£45,440	6.56	6.56	£10,692	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1b treatment-experienced cirrhotic IFN-ineligible

In this scenario SOF+DCV+RBV 24 weeks was included as an additional comparator. SVR data for SOF+DCV+RBV in GT1 treatment-experienced cirrhotic patients was used (see SVR Table 105), but it was assumed that all other data was equal to SOF+DCV+RBV 24 weeks in GT3 treatment-experienced cirrhotic patients.

Table 228: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,361	9.27	4.93					
Ombitasvir/paritaprevir/ritonavir + dasabuvir + RBV (12 wks)	£55,073	16.60	9.66	£19,712	7.33	7.33	£4,167	£4,167
Sofosbuvir/velpatasvir (12 wks)	£58,342	16.45	9.58	£22,981	7.18	7.18	£4,942	Dominated
Ledipasvir/sofosbuvir (12 wks)	£60,288	15.75	9.12	£24,927	6.48	6.48	£5,949	Dominated
Sofosbuvir + daclatasvir + RBV (24 wks)	£79,824	16.52	9.61	£44,463	7.25	7.25	£9,501	£39,869

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1 treatment-naïve cirrhotic IFN-ineligible

In this scenario SOF+DCV+RBV 24 weeks was included as an additional comparator. SVR data for SOF+DCV+RBV in GT1 treatment-naïve cirrhotic patients was used (see SVR Table 98), but it was assumed that all other data was equal to SOF+DCV+RBV 24 weeks in GT3 treatment-experienced cirrhotic patients.

Table 229: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
Sofosbuvir/velpatasvir (12 wks)	£47,161	17.34	10.11	£11,371	7.98	7.98	£2,217	£2,217
Ledipasvir/sofosbuvir (12 wks)	£60,349	16.98	9.88	£24,559	7.62	7.62	£5,012	Dominated
Sofosbuvir + daclatasvir + RBV (24 wks)	£81,230	15.92	9.23	£45,440	6.56	6.56	£10,692	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT1 treatment-experienced cirrhotic IFN-ineligible

In this scenario SOF+DCV+RBV 24 weeks was included as an additional comparator. SVR data for SOF+DCV+RBV in GT1 treatment-experienced cirrhotic patients was used (see SVR Table 105), but it was assumed that all other data was equal to SOF+DCV+RBV 24 weeks in GT3 treatment-experienced cirrhotic patients.

Table 230: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,361	9.27	4.93					
Sofosbuvir/velpatasvir (12 wks)	£57,869	16.65	9.71	£22,508	7.38	7.38	£4,709	£4,709
Ledipasvir/sofosbuvir (12 wks)	£60,288	15.75	9.12	£24,927	6.48	6.48	£5,949	Dominated
Sofosbuvir + daclatasvir + RBV (24 wks)	£79,824	16.52	9.61	£44,463	7.25	7.25	£9,501	£39,869

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.8.3.2 GT4 overall

GT4 treatment-naïve non-cirrhotic

In this scenario DCV+Peg-IFN+RBV 24/48 weeks and SMV+Peg-IFN+RBV (RGT) were included as additional comparators. In this scenario SVR data for SMV and DCV regimens in GT4 patients was used (see SVR Table 117) but it was assumed that all other data was equal to SMV+Peg-IFN+RBV RGT in GT1 treatment-naïve non-cirrhotic patients.

Table 231: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£15,956	19.09	13.75					
Peg-IFN + RBV (48 wks)	£20,510	20.45	15.32	£4,554	1.36	1.36	£2,901	£2,901
Daclatasvir + Peg-IFN + RBV (daclatasvir 24w + Peg-IFN/RBV for 48w)	£29,713	21.73	17.10	£13,757	2.64	2.64	£4,107	£5,170
Simeprevir + Peg-IFN + RBV RGT	£33,446	21.47	16.70	£17,490	2.38	2.38	£5,929	Dominated
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	£36,192	21.91	17.31	£20,236	2.82	2.82	£5,684	£4,502
Sofosbuvir/velpatasvir (12 wks)	£41,682	21.91	17.32	£25,726	2.82	2.82	£7,206	£9,123

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT4 treatment-naïve cirrhotic

In this scenario DCV+Peg-IFN+RBV 24/48 weeks, SMV+Peg-IFN+RBV (RGT) and OBV/PTV/RTV+RBV 24 weeks were included as additional comparators. In this scenario SVR data for SMV and DCV regimens was used (see SVR Table 117) but it was assumed that all other data was equal to SMV+Peg-IFN+RBV RGT in GT1 treatment-naïve cirrhotic.

For OBV/PTV/RTV+RBV 24 weeks, in the absence of SVR rates, all data was assumed equivalent to OBV/PTV/RTV+DSV+RBV 24 weeks in GT1a treatment-naïve cirrhotic.

Table 232: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
Peg-IFN + RBV (48 wks)	£43,342	11.79	6.43	£7,552	2.43	2.43	£5,208	£5,208
Simeprevir + Peg-IFN + RBV RGT	£54,753	14.89	8.47	£18,963	5.53	5.53	£5,434	£5,594
Ledipasvir/sofosbuvir (12 wks)	£58,936	17.45	10.18	£23,146	8.09	8.09	£4,451	£2,446
Sofosbuvir/velpatasvir (12 wks)	£59,344	17.45	10.18	£23,554	8.09	8.09	£4,530	Dominated
Daclatasvir + Peg-IFN + RBV (daclatasvir 24w + Peg-IFN/RBV for 48w)	£60,349	16.98	9.88	£24,559	7.62	7.62	£5,012	£3,223
Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)	£92,126	16.96	9.84	£56,336	7.60	7.6	£11,592	£7,413

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT4 treatment-experienced non-cirrhotic

In this scenario DCV+Peg-IFN+RBV 24/48 weeks, SMV+Peg-IFN+RBV (RGT) and SOF+DCV 12 weeks were included as additional comparators. In this scenario SVR data for SMV and DCV regimens was used (see SVR Table 121) but it was assumed that all other data was equal to SMV+Peg-IFN+RBV RGT in GT1 treatment-experienced non-cirrhotic patients.

For SOF+DCV 12 weeks, in the absence of SVR rates, all data was assumed equivalent to SOF+DCV 12 weeks in GT1 treatment-experienced non-cirrhotic patients.

Table 233: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£14,998	18.28	13.18					
Peg-IFN2a + RBV (48 wks)	£19,342	19.43	14.56	£4,344	1.15	1.15	£3,148	£3,148
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	£35,556	20.64	16.31	£20,558	2.36	2.36	£6,568	£9,265
Simeprevir + Peg-IFN + RBV RGT	£40,864	19.83	15.09	£25,866	1.55	1.55	£13,542	Dominated
Sofosbuvir/velpatasvir (12 wks)	£41,046	20.64	16.32	£26,048	2.36	2.36	£8,296	£148
Daclatasvir + Peg-IFN + RBV (daclatasvir 24w + Peg-IFN/RBV for 48w)	£41,891	20.53	16.17	£26,893	2.25	2.25	£8,994	£11,952
Ledipasvir/sofosbuvir (12 wks)	£42,803	20.28	15.84	£27,805	2.00	2	£10,453	£13,903
SOF+DCV (12 wks)	£61,747	20.64	16.32	£46,749	2.36	2.36	£14,888	£19,809

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT4 treatment-experienced cirrhotic

In this scenario DCV+Peg-IFN+RBV 24/48 weeks, SMV+Peg-IFN+RBV (RGT) and OBV/PTV/RTV+RBV 24 weeks were included as additional comparators. In this scenario SVR data for SMV and DCV regimens was used (see SVR Table 121) but it was assumed that all other data was equal to SMV+Peg-IFN+RBV RGT in GT1 treatment-experienced cirrhotic.

For OBV/PTV/RTV+RBV 24 weeks, in the absence of SVR rates, all data was assumed equivalent to OBV/PTV/RTV+DSV+RBV 24 weeks in GT1a treatment-experienced cirrhotic.

Table 234: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,361	9.27	4.93					
Peg-IFN + RBV (48 wks)	£41,977	11.54	6.29	£6,616	2.27	2.27	£4,865	£4,865
Ledipasvir/sofosbuvir (12 wks)	£57,295	16.76	9.78	£21,934	7.49	7.49	£4,522	£4,389
Sofosbuvir/velpatasvir (12 wks)	£57,712	16.76	9.78	£22,351	7.49	7.49	£4,608	Dominated
Simeprevir + Peg-IFN + RBV RGT	£62,373	13.14	7.31	£27,012	3.87	3.87	£11,350	Dominated
Sofosbuvir + Peg-IFN + RBV (12 wks)	£65,386	13.06	7.35	£30,025	3.79	3.79	£12,407	£7,922
Daclatasvir + Peg-IFN + RBV (daclatasvir 24w + Peg-IFN/RBV for 48w)	£79,323	15.38	8.76	£43,962	6.11	6.11	£11,478	£7,195
Ombitasvir/paritaprevir/ritonavir + RBV (24 wks)	£90,077	16.50	9.58	£54,716	7.23	7.23	£11,767	£7,568

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.8.3.3 GT4 IFN-ineligible

GT4 treatment-naïve non-cirrhotic IFN-ineligible

In this scenario SOF+DCV 12 weeks was included as an additional comparator. In this scenario, in the absence of SVR rates, all data was assumed equivalent to SOF+DCV 12 weeks in GT1 treatment-naïve non-cirrhotic patients.

Table 235: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£15,956	19.09	13.75					
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	£36,192	21.91	17.31	£20,236	2.82	2.82	£5,684	£5,684
Sofosbuvir/velpatasvir (12 wks)	£41,682	21.91	17.32	£25,726	2.82	2.82	£7,206	£549,000
Sofosbuvir + daclatasvir (12 wks)	£62,383	21.91	17.32	£46,427	2.82	2.82	£13,005	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT4 treatment-naïve cirrhotic IFN-ineligible

In this scenario SOF+DCV+RBV 24 weeks was included as an additional comparator. In this scenario, in the absence of SVR rates, all data was assumed equivalent to SOF+DCV+RBV 24 weeks in GT3 treatment-experienced cirrhotic patients.

Table 236: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
Ledipasvir/sofosbuvir (12 wks)	£58,936	17.45	10.18	£23,146	8.09	8.09	£4,451	£4,451
Sofosbuvir/velpatasvir (12 wks)	£59,344	17.45	10.18	£23,554	8.09	8.09	£4,530	Dominated
Sofosbuvir + daclatasvir + RBV (24wks)	£84,651	14.48	8.29	£48,861	5.12	5.12	£14,762	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT4 treatment-experienced non-cirrhotic IFN-ineligible

In this scenario SOF+DCV 12 weeks was included as an additional comparator. In this scenario, in the absence of SVR rates, all data was assumed equivalent to SOF+DCV 12 weeks in GT1 treatment-experienced non-cirrhotic patients.

Table 237: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£14,998	18.28	13.18					
Ombitasvir/paritaprevir/ritonavir + RBV (12 wks)	£35,556	20.64	16.31	£20,558	2.36	2.36	£6,568	£6,568
Sofosbuvir/velpatasvir (12 wks)	£41,046	20.64	16.32	£26,048	2.36	2.36	£8,296	£549,000
Ledipasvir/sofosbuvir (12 wks)	£42,803	20.28	15.84	£27,805	2.00	2	£10,453	Dominated
Sofosbuvir + daclatasvir (12 wks)	£61,747	20.64	16.32	£46,749	2.36	2.36	£14,888	£39,467

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

GT4 treatment-experienced cirrhotic IFN-ineligible

In this scenario SOF+DCV+RBV 24 weeks was included as an additional comparator. In this scenario, in the absence of SVR rates, all data was assumed equivalent to SOF+DCV+RBV 24 weeks in GT3 treatment-experienced cirrhotic patients.

Table 238: Scenario results (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,361	9.27	4.93					
Ledipasvir/sofosbuvir (12 wks)	£57,295	16.76	9.78	£21,934	7.49	7.49	£4,522	£4,522
Sofosbuvir/velpatasvir (12 wks)	£57,712	16.76	9.78	£22,351	7.49	7.49	£4,608	Dominated
Sofosbuvir + daclatasvir + RBV (24wks)	£84,651	14.48	8.29	£49,290	5.21	5.21	£14,670	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

5.8.4 *Summary of sensitivity analyses results*

The PSA results have been summarised in Section 5.8.1.3.

Across the DSA conducted, the economic results were found to be sensitive to treatment costs, SVR rates for SOF/VEL and the selected comparator, and the discount rate applied. The latter parameter is to be expected given the long time horizon employed in the model due to the life long and chronic nature of CHC. The key drivers and their impact on ICERs are reported in more detail in Section 5.8.2.2.

Scenario analyses were conducted in GT1 and GT4 to include a small number of comparator treatments that were not included in the base-case incremental results for the reasons outlined in Section 5.8.3. In order to include these comparator treatments, assumptions were required to enable the model to be appropriately modified. These assumptions and results are clearly reported in Section 5.8.3.

In GT1 IFN-ineligible patient indications, SOF+DCV+RBV 24 weeks was added as a comparator. The significant treatment costs of administering this treatment for 24 weeks means it was dominated by SOF/VEL or had an ICER >£30,000 per QALY in all GT1 IFN-ineligible indications.

In GT 4, SOF/VEL was cost-effective in non-cirrhotic patients, producing incremental and vs baseline ICERs <£10,000 per QALY in both treatment-naïve and -experienced patients. In GT4 IFN ineligible patients, SOF/VEL was dominated or produced an ICER >£30,000 per QALY vs all additional comparators.

5.9 *Validation*

5.9.1 *Validation of de novo cost-effectiveness analysis*

The model underwent internal and external validation.

The internal validation was conducted by a senior health economist. Three specific tasks were undertaken. Firstly, the model was assessed using the Phillips et al, (2004) (199) 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.

For the external validation, KOL input was sought to validate major assumptions in the SOF/VEL model. An external health economist undertook a comprehensive validation of the assumptions and results of the model.

5.10 *Interpretation and conclusions of economic evidence*

5.10.1 *Are the results from this economic evaluation consistent with the published economic literature?*

There are no published economic models exploring the cost-effectiveness of any SOF/VEL-based regimen in CHC.

5.10.2 *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 economic evaluation are relevant to all groups of patients, defined in Section 5.2.1, as the clinical data included in the model directly reflects that from the Phase II and III clinical trials in these patients.

The economic evaluation also provides comprehensive evidence for GT1–4 patients who are IFN-ineligible.

5.10.3 *Strengths, limitations and generalisability of the analysis*

Strengths of the evaluation

The modelling approach was deemed the most adequate to reflect 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 regimen.

The model structure is similar to that used in previous cost-effectiveness analyses and NICE CHC appraisals, including LDV/SOF (TA363) and SOF (TA330). As with these NICE appraisal models, a 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 structure reflects comments made by the Evidence Review Group for the LDV/SOF NICE submission, which include the following:

- Undertaking a targeted literature review and incorporating genotype-specific TP estimates from the non-cirrhotic to compensated-cirrhotic health state. This avoids the previously criticised method used to estimate this TP for LDV/SOF and reflects the current literature on the speed of disease progression in CHC.
- Undertaking a review of costs and utility values to inform the model's parameters
- Providing clarity on the way in which SVR rates from clinical trials have been identified and for each patient population and comparator in the model
- Improving the transparency in the model and report about how PSA distributions are used

A number of other significant modelling changes were made in light of the LDV/SOF submission, which include attempts to improve the usability and transparency of the economic model. These included:

- Modelling non-cirrhotic and cirrhotic patients separately
- Modelling GT4/5/6 patients separately

The model has included all important health effects, that is, SVRs, AEs and HRQL. The model has been populated with clinical data from Phase III clinical trials on SOF/VEL, providing a direct comparison between the currently available treatments in the NHS for each patient group and the licensed dose of SOF/VEL. 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. A systematic literature review was also conducted to obtain information on relevant economic evaluations, utilities, TPs, health state costs and resource use. 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.

Extensive deterministic and probabilistic sensitivity analyses were conducted. For the DSA, tornado diagrams were presented and the key drivers on the base-case ICER were reported. A comprehensive PSA was conducted to quantify parameter uncertainty and determine the probability of SOF/VEL being cost-effective. In general, 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 model was thoroughly validated by two internal health economists, a statistician, an external health economist and a clinical expert validated the model's clinical inputs.

Weaknesses of the evaluation

Similar to the sofosbuvir and LDV/SOF NICE submissions, no robust NMA was possible for SOF/VEL. As described in Section 4.10, an attempt to derive a robust network meta-analysis was made for the GT1 TN and GT3 TN populations, but it was not possible to generate clinically valid estimates of relative efficacy stratified by treatment history, sub genotype and fibrosis stage. For this reason, the NMA could not be considered appropriate for the economic model. It was therefore considered more appropriate to populate the economic model with efficacy data from individual studies in all patient groups. This allowed the economic model to be populated with efficacy data that was stratified by treatment history and cirrhosis status where the data allowed, an approach which was felt to be more transparent and in line with the requirements of the NICE scope.

In the absence of patient-level data from the ASTRAL trials, the treatment-related utility decrement for patients treated with SOF/VEL was assumed to be equal to those from the LDV/SOF ION trials. This assumption is conservative, because of the superior SVR rates of SOF/VEL in the ASTRAL studies compared to LDV/SOF in the ION trials.

The calculation of treatment costs in the model is based on the average treatment duration for that treatment in the specific patient group. However, treatment costs were included in the sensitivity analysis to explore the impact of increasing and decreasing the total treatment cost by +/- 25%. The enabled elements such as changes in the treatment duration, wastage, monitoring and adverse events to be captured.

The economic analysis does not consider re-infection once a person achieves an SVR, which may not appropriately reflect the life of some patients with CHC. This may over-estimate the cost-effectiveness of all active treatments within the model. However, the model does not consider the reduction of HCV transmission due to improved treatment success associated with SOF/VEL relative to current treatment options. The potential benefit of SOF/VEL in alleviating the public health burden of CHC in England is therefore likely to be underestimated.

5.10.4 *What further analyses could be carried out to enhance the robustness or completeness of the results?*

The impact of reducing the onwards transmission of HCV has not been incorporated in this economic evaluation. This evaluation therefore underestimates the QALY gain and wider societal benefit that will be observed following the introduction of SOF/VEL. Allowing for this in the model, fewer transmissions would occur as a result of the higher cure rate, and therefore patients would experience high QALYs and costs to the NHS will be reduced.

The impact of having a highly effective and cost-effective pan-genotypic therapy for CHC may have significant implications for the diagnostic pathway for CHC patients. The potential cost-benefits of removing diagnostic elements that are not required have not been factored into this analysis.

6 Assessment of factors relevant to the NHS and other parties

6.1 *Population: people eligible for treatment*

Table 239: Estimation of patients eligible for treatment – GT3

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent CHC population	170,807	170,807	170,807	170,807	170,807
Patients with CHC treated each year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible for treatment: patients with GT3 CHC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHC, chronic hepatitis C; GT, genotype.

Table 240: Estimation of patients eligible for treatment – GT1

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent CHC population	170,807	170,807	170,807	170,807	170,807
Patients with CHC treated each year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible for treatment: patients with GT1 CHC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHC, chronic hepatitis C; GT, genotype.

Table 241: Estimation of patients eligible for treatment – GT2

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent CHC population	170,807	170,807	170,807	170,807	170,807
Patients with CHC treated each year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible for treatment: patients with GT2 CHC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHC, chronic hepatitis C; GT, genotype.

Table 242: Estimation of patients eligible for treatment – GT4–6

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent CHC population	170,807	170,807	170,807	170,807	170,807
Patients with CHC treated each year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible for treatment: patients with GT4/5/6 CHC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHC, chronic hepatitis C; GT, genotype.

6.1.1 *Assumptions*

- Adult population in England; 42,701,800 (200)

- Prevalence of chronic CHC infection in England: 0.4% (3)
- The budget impact analysis presented is based on a constant proportion of patients with chronic CHC who are treated per year in England (7.5%) (201). While it is possible that the proportion of patients who are treated will gradually increase over time, as assumed in the TA365 costing template, there appears to be no literature that currently supports this. Moreover, it is plausible that the total prevalence of CHC will decrease over time given access to highly effective therapies such as SOF/VEL. The budget impact analyses therefore assumes a constant population over the 5-year time horizon of the model, which is consistent with other budget impact analyses for NICE appraisal of CHC therapies (LDV/SOF, SOF).
- Genotype split (3):
  - GT3: 44%
  - GT1: 47%
  - GT2: 5.5% (assumes the ratio of GT2, GT4, GT5 and GT6) is the same in England (not reported) as it is in Northern Ireland (reported)
  - GT4–6: 3.5% (assumes the ratio of GT2, GT4, GT5 and GT6) is the same in England (not reported) as it is in Northern Ireland (reported)
- Proportion of patients who are treatment experienced (201):
  - GT3: 24%
  - GT1: 19%
  - GT2: 18%
  - GT4–6: 21%
- Proportion of patients who have compensated cirrhosis (as per LDV/SOF submission TA363):
  - GT3: 25%
  - GT1: 21%
  - GT2: 21% (assumed equal to GT1)
  - GT4–6: 21% (assumed equal to GT1)

6.2 *Costs included*

The anticipated uptake of SOF/VEL across a 5-year time horizon is indicated in Table 243.

Table 243: Estimated uptake of SOF/VEL

Genotype	Year 1	Year 2	Year 3	Year 4	Year 5
GT3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GT1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GT2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GT4–6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GT, genotype.

Current treatment options considered in the budget impact analysis are described in Table 244 and are consistent with the comparators used in the cost-utility analysis.

Table 244: SOF/VEL comparators for each CHC genotype

Comparator	GT3	GT1	GT2	GT4–6
LDV/SOF		X		X
No treatment	X	X	X	X
OBV/PTV/RTV±DSV±RBV		X		X
Peg-IFN+RBV	X	X	X	X
SMV+Peg-IFN+RBV		X		X
SOF+DCV±RBV	X	X		
SOF+Peg-IFN+RBV	X	X		X
SOF+RBV	X		X	

Abbreviations: DCV, daclatasvir; DSV, dasabuvir; GT, genotype; LDV, ledipasvir; OBV, ombitasvir; Peg-IFN, pegylated interferon; PTV, paritaprevir; RTV, ritonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

The level of displacement of each SOF/VEL comparator is assumed to be constant over time. The displacement for each comparator within each genotype/patient group is described in Table 245.

Table 245: SOF/VEL comparator displacement

Comparator	GT3	GT1	GT2	GT4–6
LDV/SOF	-	[redacted]	-	[redacted]
No treatment	[redacted]	[redacted]	[redacted]	[redacted]
OBV/PTV/RTV±DSV±RBV	-	[redacted]	-	[redacted]
Peg-IFN+RBV	[redacted]	[redacted]	[redacted]	[redacted]
SMV+Peg-IFN+RBV	-	[redacted]	-	[redacted]
SOF+DCV±RBV	[redacted]	[redacted]	-	-
SOF+Peg-IFN+RBV	[redacted]	[redacted]	-	[redacted]
SOF+RBV	[redacted]	-	[redacted]	-

Abbreviations: DCV, daclatasvir; DSV, dasabuvir; GT, genotype; LDV, ledipasvir; OBV, ombitasvir; Peg-IFN, pegylated interferon; PTV, paritaprevir; RTV, ritonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

Treatment costs used in budget impact calculations are consistent with treatment costs used in the cost-utility analysis; references are provided in Table 83. Treatment durations for all treatment regimens are as reported in Section 5.6.1. Drug costs were taken from the BNF March 2016.

There are no other significant costs associated with SOF/VEL regimens displacing existing CHC treatments.

6.3 *Resource savings*

There are several sources of cost savings which could be realised with the introduction of SOF/VEL regimens.

Less monitoring should be required with SOF/VEL regimens compared with currently available regimens and hence lead to resource savings. Firstly, there is no requirement for response guided therapy as there is with Peg-IFN or first generation PI-based therapies, removing the need for regular on-treatment viral load monitoring and clinic visits. Secondly, adverse event monitoring and management of AEs should also be reduced. For example, as the first pan-genotypic STR, offering very high SVR rates across all HCV genotypes, SOF/VEL completely eliminates the healthcare costs and resource utilisation required to manage AEs that occur on treatment with Peg-IFN and RBV, in the majority of circumstances. Thirdly, SOF/VEL reduces the need for, and infrastructure costs associated with HCV genotyping. This is likely to be of particular value in resource-limited healthcare settings where rapid genotyping is not feasible (for example, prisons) or where the results of genotyping may be difficult to interpret.

Since SOF/VEL is generally associated with higher SVR rates compared to many comparators, the costs associated with the management of patients who do not achieve an SVR are also projected to decrease.

6.4 *Budget impact*

6.4.1 *Budget impact – GT3*

The net total budget impact for GT3 patients is described in Table 246. SOF/VEL is anticipated to have a positive budget impact in England for patients with GT3 CHC. Key drivers for this budget impact are:

- The large number of patients treated in this population
- High proportion of displaced Peg-IFN+RBV regimen which has a – treatment cost of £5,115 as a weighted average across GT3 patients.
- High proportion of displaced SOF+Peg-IFN+RBV which has a – treatment cost of £16,162 as a weighted average across GT3 patients.
- Different ‘net total budget impact’ over time due to anticipated variations in market share described in Table 243.

Table 246: Budget impact – GT3

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced medicines cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net additional medicines savings/costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated in each year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NET TOTAL BUDGET IMPACT	**£8,650,176**	**£6,217,314**	**£6,848,056**	**£6,848,056**	**£6,848,056**

6.4.2 *Budget impact – GT1*

The net total budget impact for GT1 patients is described in Table 247. SOF/VEL is anticipated to have a small negative (cost-saving) impact in England for patients with GT1 CHC. Key drivers for this negative budget impact are:

- High proportion of displaced OBV/PTV/RTV+DSV regimen which costs £40,061 as a weighted average across GT1 patients.
- High proportion of displaced LDV/SOF which costs £30,600 as a weighted average across GT1 patients.
- Different 'net total budget impact' over time due to anticipated variations in market share described in Table 243.

Table 247: Budget impact – GT1

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced medicines cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net additional medicines savings/costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated in each year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NET TOTAL BUDGET IMPACT	**-£827,431**	**-£1,034,288**	**-£1,034,288**	**-£1,034,288**	**-£1,034,288**

6.4.3 *Budget impact – GT2*

The net total budget impact for GT2 patients is described in Table 248. SOF/VEL is anticipated to have a positive budget impact in England for patients with GT2 CHC. Key drivers for this budget impact are:

- High proportion of displaced Peg-IFN+RBV regimen which has a – treatment cost of £4,903 as a weighted average across GT2 patients.
- High proportion of displaced SOF+RBV which has a – treatment cost of £6,858 as a weighted average across GT2 patients.
- Different 'net total budget impact' over time due to anticipated variations in market share described in Table 243.

Table 248: Budget impact – GT2

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced medicines cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net additional medicines savings/costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated in each year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NET TOTAL BUDGET IMPACT	**£5,360,933**	**£5,604,612**	**£6,173,196**	**£6,173,196**	**£6,173,196**

6.4.4 *Budget impact – GT4–6*

The net total budget impact for GT4–6 patients is described in Table 249. SOF/VEL is anticipated to have a positive budget impact in England for patients with GT4–6 CHC. Key drivers for this budget impact are:

- High proportion of displaced LDV/SOF regimen which has a – treatment cost of £14,584 as a weighted average across GT4–6 patients.
- High proportion of displaced Peg-IFN+RBV which has a – treatment cost of £8,329 as a weighted average across GT4–6 patients.
- Different 'net total budget impact' over time due to anticipated variations in market share describe in Table 243.

Table 249: Budget impact – GT4–6

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced medicines cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net additional medicines savings/costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated in each year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NET TOTAL BUDGET IMPACT	**£657,896**	**£657,896**	**£657,896**	**£657,896**	**£657,896**

6.5 *Additional factors not included in analysis*

The short time horizon of the budget impact model fails to capture savings caused by avoiding more severe health states that take a longer time to occur, such as decompensated cirrhosis, HCC and liver transplants. The long term outcomes could also mean an eradication to HCV-induced HCC and HCV-related liver transplant, since both of these events stem from cirrhotic patients which have to date proven to be a very difficult to treat population.

We have also not included any of the costs associated with adverse events, monitoring and costs of managing patients on waiting lists. In addition, as the first pan-genotypic STR, offering very high SVR rates across all HCV genotypes, SOF/VEL reduces the need for, and infrastructure costs associated with HCV genotyping. This is likely to be of particular value in resource-limited healthcare settings where rapid genotyping is not feasible (for example, prisons) or where the results of genotyping may be difficult to interpret.

In addition, given that SOF/VEL is a pan-genotypic STR, with high efficacy, short treatment duration and excellent tolerability profile, it offers the potential for a substantial long-term public health benefit, by preventing onwards transmission in higher risk patient populations. This can enable significant and lasting progress to be made towards the goal of eliminating CHC as a public health concern in the UK. However, this benefit is not possible to capture in a budget impact model.

7 References

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8 Appendices

Appendix 1: SmPC and EPAR

Appendix 2: Summary of EASL recommendations for hepatitis C

Appendix 3: Search strategy for relevant studies

Appendix 4: Quality assessment of RCTs for SOF/VEL

Appendix 5: Subgroup analyses from RCTs

Appendix 6: Studies identified in the clinical systematic review which compared Peg-IFN regimens only

Appendix 7: Networks and studies excluded from NMA

Appendix 8: Quality assessment of studies used in naïve comparison

Appendix 9: Programming language used in the indirect/mixed treatment comparisons

Appendix 10: NMA sensitivity analyses

Appendix 11: SVR calculations for Peg-IFN+RBV from Lagging/Shoeb studies

Appendix 12: Search strategy for cost-effectiveness studies

Appendix 13: Quality assessment of cost-effectiveness studies

Appendix 14: Probability of death

Appendix 15: Targeted literature search for studies informing the annual transition probability from non-cirrhotic to compensated cirrhosis health states

Appendix 16: Search strategy for measurement and valuation of health effects

Appendix 17: Cost and healthcare resource identification, measurement and valuation

Appendix 18: Markov traces

Appendix 19: Checklist of confidential information

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Single technology appraisal

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

Dear [redacted],

The Evidence Review Group, Kleijnen Systematic Reviews Ltd, and the technical team at NICE have looked at the submission received on 20 May 2016 from Gilead. 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 **Monday 4 July 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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 Sophie Laurenson, Technical Lead (Sophie.Laurenson@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

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Section A: Clarification on literature searching

A1. For all searches, please provide the date span* (e.g. Medline 1946-2016/01/13) for each individual database searched. **Please note the date span will not be the same as the date the searches were conducted*.

A2. **Priority question:** Please clarify why the clinical effectiveness searches were limited by date from 2006 to date of searching.

A3. Please clarify why search terms for the following drugs that are not specified in the NICE scope were included in the clinical effectiveness searches (asunaprevir, grazoprevir, faldaprevir and elbasvir).

A4. Please clarify why, in the clinical effectiveness searches, free-text search lines were limited to different fields in Medline (.mp. suffix) than in Embase (.ti,ab. suffix).

A5. **Priority question:** Please clarify why, in the clinical effectiveness searches, Emtree indexing terms for the population and drugs facets in the Embase search were restricted to focus (i.e. only Major Emtree indexing heading terms would be retrieved).

A6. **Priority question:** Please explain why the EMTREE indexing term "hepatitis C, chronic" was not included in the Embase search strategy for the clinical effectiveness searches? We note that this omission may have failed to retrieve up to 2,126 references (15.6.16).

☐	4	hepatitis C/	85321	Advanced
☐	5	chronic hepatitis c/	2482	Advanced
☐	6	5 not 4	2126	Advanced

A7. Please clarify why, in the clinical effectiveness searches, the Embase search was limited to remove conference abstracts and papers (Appendix 3, page 10, lines 66-69). There is no explanation in the reported search methods for a limit on publication type or status (company submission, page 60).

A8. Please clarify how reports of adverse events were identified. If separate adverse event searches were conducted, please report full search methods and provide full search strategies for each resource searched.

A9. **Priority question:** In the clinical effectiveness searches, a separate search to identify references from specific conference proceedings was reported (Appendix 3,

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pages 13-14), which retrieved 962 records for screening. These search results have not been included in the PRISMA flowchart in Section 4.1.2, page 62 of the company submission. Please provide a revised PRISMA flowchart incorporating these search results, and providing details of inclusion and reasons for exclusion.

A10. **Priority question:** For all cost-effectiveness, measurement and valuation of health effects, and health resource identification searches, please provide the number of records, or hits, retrieved by each line in each search strategy at the date of searching.

A11. **Priority question:** Please explain why search terms for peginterferon alfa, daclatasvir, paritaprevir, ritonavir and ribavirin were not included in the cost-effectiveness search strategies (Appendix 12), when these drugs are listed as comparators in the NICE Scope.

A12. **Priority question:** Please clarify why search terms for the following drugs that are not specified in the NICE scope were included in the cost-effectiveness searches (danoprevir, elbasvir and grazoprevir).

A13. **Priority question:**

a. Please clarify why an economic evaluations limit was applied to the NHS EED search in Appendix 12. This is considered to be too restrictive.
b. Please assess and confirm which records have been lost.

A14. Please provide the search terms and numbers of results for the conference abstract searching reported in Appendix 12.4.

A15. Please provide the search terms and numbers of results for the conference abstract searching reported in Appendix 16.4.

A16. Please check the date limits applied to the Medline search in Table 25 (Appendix 17.3); specifically the two different date limits applied to lines 44 and 48. Please provide an explanation of the intended outcomes of these limits.

A17. **Priority question:**

a. Please clarify why a costs/economics limit was applied to the NHS EED search in appendix 17 (Table 26, lines 4-36). This is considered to be overly restrictive.
b. Please assess and confirm which records have been lost.

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Section B: Clarification on effectiveness data

B1. **Priority question:** Please provide the data that was used in each WinBUGS MTC model in the WinBUGS format (ideally as an Excel spreadsheet).

B2. **Priority question:** Table 39 provides the sources for the SVR inputs in the economic model. However, the company have selected one study for each SVR, even when multiple sources are available, and in some cases, the justification does not seem appropriate.

a. Please provide a meta-analysis (using a standard method such as inverse variance) of SVR and safety rates (i.e. treatment-related adverse events), one for each treatment in each subgroup using all sources of data available.

b. Please provide further justification why certain studies were selected and not others.

i. For instance, under 'GT3 TN (NC and CC)', second row: SOF+RBV 24w, ASTRAL-3 was chosen because it has a head-to-head comparison with SOF/VEL 12w; however, BOSON has a head-to-head comparison with SOF+Peg-INF+RBV 12w which is also in the network and would therefore be just as appropriate; please explain why BOSON was not chosen.

ii. Similarly, for SOF+DCV 12w (page 132), ALLY-3 was chosen, but it is not clear why AI444040 would not be equally appropriate.

c. For SOF+DCV+RBV 24w (page 132) there are no data, so data for SOF+DCV 12w from ALLY3 are used. Please confirm that the company searched for all possible study types including case series, for evidence for SOF+DCV+RBV 24w?

d. For Peg-IFN+RBV 24w (page 132), there is a rational presented for using FISSION. However, this rational suggests that there might be other relevant sources.

i. Please clarify which other relevant sources there are.

ii. And please clarify in general whether all possible sources for each treatment/population have been listed (including all study types) in Table 39.

e. For Peg-IFN+RBV 24w in GT3 TE (NC and CC) (page 131), these data should correspond with the same intervention in Table 94, page 232. However, in Table 94, Peg-IFN+RBV 48w is listed.

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i. Please clarify this discrepancy in the treatment duration?

ii. Please clarify what is meant by 'accepted' in the sentence "Accepted previously in NICE TA330 for SOF" (page 131). Please confirm whether NICE specifically agreed that this was acceptable?

Section C: Clarification on cost-effectiveness data

Cost effectiveness review

C1. Details and results of the following studies have not been extracted in the cost effectiveness review performed in the company submission. It is not clear why these studies were not extracted. In particular, the rationale: 'Does not include DAA regimens of particular interest' does not seem valid when applied to studies with appropriate comparators (for example, Cure et al, 2014, which studied telaprevir in combination with pegylated interferon alpha and ribavirin in previously untreated chronic hepatitis C genotype 1 patients). Please extract data from the following studies as performed in Table 15 of Appendix 12.

a. Cure S, Bianic F, Gavart S, et al. Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in previously untreated chronic hepatitis C genotype 1 patients. Journal of Medical Economics 2014;17:65-76.

b. Cure S, Bianic F, Gavart S, et al. Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in treatment-experienced chronic hepatitis C genotype 1 patients. Journal of Medical Economics 2014;17:77-87.

c. Westerhout K, Treur M, Mehnert A, et al. A cost utility analysis of simeprevir used with peginterferon + ribavirin in the management of genotype 1 hepatitis C virus infection, from the perspective of the UK National Health Service. Journal of Medical Economics 2015;18:838-849.

d. National Institute for Health and Care Excellence (NICE). Sofosbuvir for treating chronic hepatitis C (TA330). 2015.

e. National Institute for Health and Care Excellence (NICE). Boceprevir for the treatment of genotype 1 chronic hepatitis C (TA253). 2012.

f. National Institute for Health and Care Excellence (NICE). Telaprevir for the treatment of genotype 1 chronic hepatitis C (TA252). 2012.

g. National Institute for Health and Care Excellence (NICE). Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C (TA331). 2015.

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Excel model

C2. The Excel model provided contains multiple hidden rows, hidden columns, hidden worksheets and cells with a white background containing white text (that is, these are not visible).

a. Please unhide all rows, columns, worksheets and make all text in cells visible (for example, changing the font colour from white to black for cells with a white background).

C3. Only two comparators can be considered simultaneously in the economic model, please provide a description of the methods used to construct CEACs including all comparators for each subgroup (including the technical implementation in the Excel file).

Model structure

C4. In Figure 16, page 192 of the company submission, there should be a connection between the compensated cirrhosis and hepatocellular carcinoma health states. Please confirm this and provide a corrected version of Figure 16.

C5. During the on-treatment period, patients are not allowed to die or to transit to more advanced disease stages (for example compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma).

a. Please include background mortality during the on-treatment period in the cost effectiveness analysis;

b. Please provide the results of all base case analyses for all subgroups presented in the company submission based on this amendment of the cost effectiveness model;

c. Please provide the results of all further analyses requested in this clarification letter based on this amendment of the cost effectiveness model.

C6. During the on-treatment period and the period between the end of treatment and the SVR assessment, patients are not allowed to progress to more advanced disease stages.

a. Please justify why patients are not allowed to progress to more advanced disease stages during these periods.

b. Please show the impact of this model assumption on the results through a sensitivity analysis where patients are allowed to progress to more advanced disease stages during the on-treatment period and the period between the end of treatment and the SVR assessment.

C7. Several model structure assumptions have been made that are inconsistent with previous health economic models.

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a. Please justify why no transition between hepatocellular carcinoma and liver transplant is incorporated in the base case.

b. Please justify why no transition was incorporated for “SVR non-cirrhotic” to “non-cirrhotic” in the base case. Similarly for “SVR cirrhosis” to “cirrhosis” and “SVR decompensated cirrhosis” to “decompensated cirrhosis”.

c. Please justify how the values used in the sensitivity analyses (presented in Table 219 of the company submission) regarding the above assumptions (see C7b; and described below Figure 16 of the company submission) are selected.

d. Please clarify what the expected impact of not distinguishing between no cirrhosis and mild cirrhosis (that is, combining METAVIR scores F0 – F3 in one health state) would be on the results.

Comparators

C8. Page 198 of the company submission states “Some comparators of relevance to the decision problem were not included in the original economic model, and because of the way in which the economic model was constructed it was not possible to introduce these into the base-case analyses.” It is not clear what the company meant by this statement and which comparators are referred to.

a. Please clarify which comparators are being referred to and provide specific reasons why the construction of the economic model did not allow to incorporate these comparators in the base case;

Treatment effectiveness

C9. **Priority question** The company selected one study for each estimate of treatment duration in the economic model.

a. Please provide a random effect meta-analyses to obtain estimates of treatment duration for the economic model, for each comparator in each subgroup;

b. Please provide a new cost-effectiveness analysis based on the pooled estimates of SVR and safety as requested in B2a and the above requested pooled estimates of treatment duration

c. Please provide a full explanation why some studies were selected and others not for these meta-analyses.

d. Please also provide the requested analyses in C9a to C9c for comparators considered in scenario analyses only.

Health related quality of life

C10. Please provide the rationale for the choice of the utility data from Wright et al (2006), apart from the fact that it was used in previous health technology appraisals.

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C11. Please provide SF-36 utility data from the ASTRAL trials and use these data in a scenario analysis.

C12. During the on-treatment period, a treatment-specific utility increment/decrement is applied to the health state utility of patients:

a. Please justify why a multiplicative approach has been used to estimate on-treatment utility increment/decrement (and not an additive approach);

b. Please justify on which evidence these treatment-specific utility increments/decrements are based;

c. Please provide scenario analyses for all subgroups showing the impact of removing all treatment-specific utility increments/decrements.

C13. Patients accomplishing sustained virological response are attributed a 0.04 utility increment.

a. Please justify on which evidence this increment is based (primary source) and why it applies in the current situation.

Resource use and costs

C14. Health state costs for the non-cirrhotic health state are based on a weighted average of 83% F0-F2 (mild) and 17% F3 (moderate) HCV patients. These figures are *"derived from HCV TherapyWatch market research data."*

a. Please justify why this source was selected and clarify why it is considered to be relevant to the current decision problem;
b. Please provide this reference and/or an active web-link to the reference.

C15. When NHS reference costs were used for resource use and costs (for example, Table 84 of the company submission)

a. Please provide the precise codes for the NHS reference costs and the precise method used to obtain the cost estimates (for example, taking a weighted average);
b. Please also provide the upper and lower quartile of the obtained estimates.

C16. Please provide adverse event management costs (as described in Table 89 of the company submission) based on NHS reference costs and use these in scenario analyses for each comparator, in each subgroup.

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Model validation

C17. **Priority question** Please perform a cross-validation of the results, by providing, for each subgroup separately, a comparison of the total life years, quality-adjusted life years and costs for each comparator included in the current assessment with previous assessments: for example, TA330, TA331, TA365, TA363, TA 364 (both ERG and Company results), the studies identified in the cost effectiveness review from the company submission (Section 5.1) and studies mentioned in Clarification Question C1.

C18. Please clarify how results of the model were externally validated (as described in Section 5.9 of the company submission).

References:

C10, Wright et al (2006): Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess. 2006 Jul;10(21):1-113, iii.

C11, ASTRAL Trials:
Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med. 2015 Dec 31;373(27):2608-17

Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med. 2015 Dec 31;373(27):2599-607.

Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N Engl J Med. 2015 Dec 31;373(27):2618-28.

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Single technology appraisal

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

Dear Ciaran,

The Evidence Review Group, Kleijnen Systematic Reviews Ltd, and the technical team at NICE have looked at the submission received on 20 May 2016 from Gilead. 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 **Monday 4 July 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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 Sophie Laurenson, Technical Lead (Sophie.Laurenson@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

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Section A: Clarification on literature searching

A1. For all searches, please provide the date span* (e.g. Medline 1946-2016/01/13) for each individual database searched. **Please note the date span will not be the same as the date the searches were conducted*.

Response

In relation to the clinical effectiveness search, the date span for all searches is provided in Table 1.

Table 1 Database date span – clinical searches

Database	Date span of search
Medline	01/01/2006 to 16/12/2015
Embase	01/01/2006 to 16/12/2015
Cochrane	01/01/2006 to 16/12/2015
Pubmed for e-pubs	01/01/2006 to 16/12/2015

Searches for cost-effectiveness evaluations, measurement and valuation of health effects and health resource identification are not specifically requested in the NICE STA template or user guide, and is not listed as an essential item in the PRISMA guidelines for the reporting of systematic reviews. Nevertheless, these searches are provided in Table 2–Table 4below.

Table 2: Cost-effectiveness Review Searches

Database	Date Span
MEDLINE and MEDLINE In-Process (via Ovid SP)	1946 – 2016/03/24
Embase (via Ovid SP)	1974 – 2016/03/23
The Cochrane Library (via the Wiley platform), including: • Cochrane Database of Systematic Reviews • Database of Abstracts of Reviews of Effects • Cochrane Central Register of Controlled Trials • HTA database • NHS Economic Evaluations Database	CDSR: Issue 3/12, Mar 2016 DARE: Issue 2/4, Apr 2015 CENTRAL: Issue 3/12, Mar 2016 HTA: Issue 1/4, Jan 2016 NHS-EED: Issue 1/4, Jan 2016 All searched 24th Mar 2016
EconLit (via EBSCO)	1886 to Feb 2016

Table 3: Measurement and Valuation of Health Effects Review Searches

Database	Date Span
MEDLINE and MEDLINE In-Process (via Ovid SP)	1946 – 2016/02/19
Embase (via Ovid SP)	1974 – 2016/02/18
The Cochrane Library (via the Wiley platform), including: • Cochrane Database of Systematic Reviews • Database of Abstracts of Reviews of Effects • Cochrane Central Register of Controlled Trials • HTA database • NHS Economic Evaluations Database	CDSR: Issue 2/12, Feb 2016 DARE: Issue 2/4, Apr 2015 CENTRAL: Issue 2/12, Feb 2016 HTA: Issue 1/4, Jan 2016 NHS-EED: Issue 1/4, Jan 2016 All searched 19th Feb 2016
EconLit (via EBSCO)	1886 to Jan 2016

Table 4: Health Resource Identification Review Searches

Database	Date Span
MEDLINE and MEDLINE In-Process (via Ovid SP)	1946 – 2016/05/11
Embase (via Ovid SP)	1974 – 2016/05/10
The Cochrane Library (via the Wiley platform), including: • HTA database • NHS Economic Evaluations Database	HTA: Issue 2/4, Apr 2016 NHS-EED: Issue 2/4, Apr 2016 All searched 11th May 2016
EconLit (via EBSCO)	1886 to Apr 2016

A2. **Priority question:** Please clarify why the clinical effectiveness searches were limited by date from 2006 to date of searching.

Response

We searched from 2006 onwards because we believe literature prior to this point would be dominated by interferon-based treatments, which are progressively becoming less relevant to UK clinical practice for the treatment of CHC. As such it was felt that literature from 2006 onwards was more likely to reflect current clinical practice and would be most informative.

A3. Please clarify why search terms for the following drugs that are not specified in the NICE scope were included in the clinical effectiveness searches (asunaprevir, grazoprevir, faldaprevir and elbasvir).

Response

This search strategy was designed prior to finalisation of the scope in March 2016. Searches were run in December 2015 but records for the treatments not of relevance to the final scope (asunaprevir, grazoprevir, faldaprevir and elbasvir) were excluded.

A4. Please clarify why, in the clinical effectiveness searches, free-text search lines were limited to different fields in Medline (.mp. suffix) than in Embase (.ti,ab. suffix).

Response

Embase assigns controlled vocabulary terms to new pharmacological treatments faster than MEDLINE. MEDLINE will often provide a 'name of substance' assignation to a new product before a controlled vocabulary term is assigned (e.g. boceprevir currently does not have a MeSH term, but is noted as a 'name of substance').

There are differences in what a mapped term (.mp) captures in Medline and Embase:

- Embase: mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword
- Medline: mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

Our Embase search uses both focused Emtree terms (rationale for focusing provided in response to A5) and free-text searches of the title and abstracts of records. Our Medline search on the other hand searches only mapped terms (.mp) which captures the MeSH term, name of substance word, title and abstract. Due to the difference between the databases we extended the free-text term search to ".mp" in Medline to capture the extra fields covered by this general field.

A5. **Priority question:** Please clarify why, in the clinical effectiveness searches, Emtree indexing terms for the population and drugs facets in the Embase search were restricted to focus (i.e. only Major Emtree indexing heading terms would be retrieved).

Response

The Cochrane handbook notes that "the pharmaceutical or pharmacological aspects of an EMBASE record are generally indexed in greater depth than the equivalent MEDLINE record." Due to extensive indexing of terms in Embase it is appropriate to focus the EMTREE terms. We used a comprehensive list of free-text terms to supplement the controlled vocabulary search.

We have retrospectively assessed if the Embase search strategy captured all the studies that ultimately were included in the SLR. The combination of our free-text terms and focussed EMTREE terms were sufficient to capture all studies available in Embase (one study was not available through Embase at all), demonstrating that the Embase search is comprehensive, independent of the Medline search.

A6. **Priority question:** Please explain why the EMTREE indexing term "hepatitis C, chronic" was not included in the Embase search strategy for the clinical effectiveness searches? We note that this omission may have failed to retrieve up to 2,126 references (15.6.16).

☐	4	hepatitis C/	85321	Advanced
☐	5	chronic hepatitis c/	2482	Advanced
☐	6	5 not 4	2126	Advanced

Response

Although this EMTREE term was not included in our search strategy we included the equivalent MeSH term in our search for Medline. This EMTREE term was only introduced on 01/05/2015 therefore any risk of failing to retrieve studies was minimal particularly as comprehensive free text terms were used and equivalent searches were run in Medline and the Cochrane Library, according to best practice, to mitigate any potential limitations to a single search.

A7. Please clarify why, in the clinical effectiveness searches, the Embase search was limited to remove conference abstracts and papers (Appendix 3, page 10, lines 66-69). There is no explanation in the reported search methods for a limit on publication type or status (company submission, page 60).

Response

The search was designed to identify full publications only; conference proceedings for the two relevant international conferences for the last two years were searched for separately. Studies presented at conferences are expected to be published as full papers within two years and therefore we excluded conference abstracts from the search as the majority were expected to be duplicates.

A8. Please clarify how reports of adverse events were identified. If separate adverse event searches were conducted, please report full search methods and provide full search strategies for each resource searched.

Response

The same search strategy was used to identify records of clinical and safety data.

A9. **Priority question:** In the clinical effectiveness searches, a separate search to identify references from specific conference proceedings was reported (Appendix 3, pages 13-14), which retrieved 962 records for screening. These search results have not been included in the PRISMA flowchart in Section 4.1.2, page 62 of the company

submission. Please provide a revised PRISMA flowchart incorporating these search results, and providing details of inclusion and reasons for exclusion.

Response

The number of conference abstracts that we included in the SLR was indicated in the flowchart in section 4.1.2 as identified from other sources (n=10). The placing of the information here was based on our interpretation of this statement from the PRISMA explanation document.

“It is useful if authors delineate for readers the number of selected articles that were identified from the different sources so that they can see, for example, whether most articles were identified through electronic bibliographic sources or from references or experts. Literature identified primarily from references or experts may be prone to citation or publication bias”.

We did not record the reasons for records excluded after preliminary screening (e.g., screening of titles and abstracts) in our PRISMA flow diagram as based on our interpretation of this explanation from PRISMA;

“The flow diagram and text should describe clearly the process of report selection throughout the review. Authors should report: unique records identified in searches; records excluded after preliminary screening (e.g., screening of titles and abstracts); reports retrieved for detailed evaluation; potentially eligible reports that were not retrievable; retrieved reports that did not meet inclusion criteria and the primary reasons for exclusion; and the studies included in the review.”

A10. **Priority question:** For all cost-effectiveness, measurement and valuation of health effects, and health resource identification searches, please provide the number of records, or hits, retrieved by each line in each search strategy at the date of searching.

Response

We are providing as much of this additional information as we can, though we wish to note that this information is not specifically requested in the NICE STA template or user guide, nor is it listed as an essential item in the PRISMA guidelines for the reporting of systematic reviews. Please see the tables below.

Cost-effectiveness Review

The number of records, or hits, retrieved by each line in each search strategy at the date of searching can be found for Ovid SP, Cochrane and EBSCO below in Table 5, Table 6 and Table 7, respectively.

Table 5: Search strategy for MEDLINE, MEDLINE In-Process and Embase (via Ovid SP) for the Cost-effectiveness Review with Number of Results Retrieved on the Date of the Search

Term group	#	Terms	No. Results
Disease area: chronic HCV	1	exp hepatitis c/	137653
	2	("hepatitis c" or hcv or "hep c").tw.	171324
	3	1 or 2	197915
Economic evaluations	4	health economics/ or exp economic evaluation/ or cost-benefit analysis/ or cost effectiveness analysis/ or cost minimization analysis/ or cost utility analysis/	374696
	5	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or consequence$)).tw.	258658
	6	((economic$ or pharmacoeconomic$) adj2 (evaluat$ or model$ or analys?s)).tw.	39563
	7	(quality adjusted life year$ or qaly$ or life year$ gained or life year$ equivalent$ or incremental cost effective$ or icer).tw.	31175
	8	or/4-7	526574
Combine	9	3 and 8	3914
HCV therapies	10	Sofosbuvir/ or (sofosbuvir or sovaldi$ or hepcinat$ or hepcvir$ or sovihep$ or harvoni$).tw.	3160
	11	Boceprevir/ or (boceprevir or victrelis$).tw.	4050
	12	Daclatasvir/ or (daclatasvir or daklinza$).tw.	1499
	13	Danoprevir/ or danoprevir.tw.	423
	14	Dasabuvir/ or (dasabuvir or exviera$).tw.	485
	15	Elbasvir/ or elbasvir.tw.	143
	16	Grazoprevir/ or (grazoprevir or zepatier$).tw.	189
	17	Ledipasvir/ or ledipasvir.tw.	1007
	18	Ombitasvir/ or (ombitasvir or viekirax$ or paritaprevir or veruprevir or viekira pak$ or technivie$).tw.	562
	19	Simeprevir/ or (simeprevir or olysio$ or galexos$ or sovriad$).tw.	1792
	20	Telaprevir/ or (telaprevir or incivo$ or incivek$ or telavic$).tw.	5464
	21	Velpatasvir/ or velpatasvir.tw.	39
	22	Direct acting antiviral/ or direct acting antivirals/ or (direct acting antiviral$ or DAA$).tw.	7438
	23	or/10-22	15076
Combined	24	9 and 23	715
Exclusion terms	25	Exp animals/ not exp humans/	8624973
	26	(comment or editorial or "case reports").pt.	3184861
	27	(case stud$ or case report$).ti.	499591
	28	Or/25-27	12075083
Combined	29	24 not 28	682
	30	**Remove duplicates from 29**	**568**

Table 6: Search strategy for The Cochrane Library (via the Wiley platform) for the Cost-effectiveness Review with Number of Results Retrieved on the Date of the Search

Term group	#	Terms	No. Results
Disease area	#1	[mh "hepatitis c"]	2554
	#2	"hepatitis c" or hcv or "hep c"	6428
	#3	#1 or #2	6428
Economic Evaluations	#4	[mh "health economics"] or [mh "economic evaluation"] or [mh "cost-benefit analysis"] or [mh "cost effectiveness analysis"] or [mh "cost minimization analysis"] or [mh "cost utility analysis"]	24730
	#5	cost* near/2 (effective* or utility* or benefit* or minimi* or consequence*)	35296
	#6	(economic* or pharmacoeconomic*) near/2 (evaluat* or model* or analys?s)	23383
	#7	("quality adjusted life year*" or qaly* or "life year* gained" or "life year* equivalent*" or "incremental cost effective*" or icer)	9376
	#8	#4 or #5 or #6 or #7	42401
Combined	#9	#3 and #8	493
HCV therapies	#10	[mh sofosbuvir] or sofosbuvir or sovaldi* or hepcinat* or hepcvir* or sovihep* or harvoni*	180
	#11	boceprevir or victrelis*	180
	#12	daclatasvir or daklinza*	67
	#13	danoprevir	44
	#14	dasabuvir or exviera*	40
	#15	elbasvir	11
	#16	Grazoprevir or zepatier*	12
	#17	ledipasvir	60
	#18	ombitasvir or viekirax* or paritaprevir or veruprevir or "viekira pak*" or technivie*	45
	#19	[mh simeprevir] or simeprevir or olysio* or galexos* or sovriad*	77
	#20	telaprevir or incivo* or incivek* or telavic*	246
	#21	velpatasvir	7
	#22	"direct acting antiviral*" or DAA*	427
	#23	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	1029
Combined	#24	#9 and #23	50
	#25	#24 in Technology Assessments and Economic Evaluations	30

Table 7: Search strategy for EconLit (via EBSCO) for the Cost-effectiveness Review with Number of Results Retrieved on the Date of the Search

Term group	#	Terms	No. Results

Term group	#	Terms	No. Results
Disease area	1	("hepatitis c" or "hep c" or "hcv").tw.	23

Measurement and Valuation of Health Effects Review

This information was not recorded and is therefore not available. However, we do have records of the total number of records sourced from each platform/database from when the database searches were performed (19th February 2016), which are shown in Table 8 below.

Table 8: Summary of the Final Number of Records from Each Database Search for the Measurement and Valuation of Health Effects Review

Platform	Database	No. Results
Ovid SP	MEDLINE, MEDLINE In-Process and other non-indexed citations, and Embase (after de-duplication using Ovid SP)	752
Cochrane Library (Wiley)	CDSR	85
	CENTRAL	130
	DARE	7
	HTA Database	10
	NHS-EED	149
	Total	**381**
EBSCO	EconLit	**23**
TOTAL		**1,156**

Health Resource Identification Review

The number of records, or hits, retrieved by each line in each search strategy at the date of searching has already been provided. Please see Table 25, Table 26, and Table 27 (Appendix 17.3) of the submission documents.

A11. **Priority question:** Please explain why search terms for peginterferon alfa, daclatasvir, paritaprevir, ritonavir and ribavirin were not included in the cost-effectiveness search strategies (Appendix 12), when these drugs are listed as comparators in the NICE Scope.

Response

Daclatasvir and paritaprevir were both included in the cost-effectiveness search strategies (lines 12 and 18 respectively in the searches of MEDLINE, Embase and the Cochrane Library).

For the treatment of HCV, ritonavir is only used in combination with ombitasvir and paritaprevir. As search terms for both of these agents were included in the search strategy, it was not deemed necessary to search for ritonavir as a separate term.

Economic evaluations were only of interest to this systematic review if they investigated the use of one or more DAA. Peg-interferon and ribavirin were only of interest as comparators to DAAs; comparisons between different formulations of interferon-based therapy, or between interferon-based therapy and no treatment, and as noted in response to A.2, interferon-based treatments are becoming significantly less relevant to UK clinical practice for the treatment of CHC, given the recent approval of DAA treatments. Therefore it was only necessary to use search terms for DAAs.

A12. **Priority question:** Please clarify why search terms for the following drugs that are not specified in the NICE scope were included in the cost-effectiveness searches (danoprevir, elbasvir and grazoprevir).

Response

The cost-effectiveness searches were conducted from a wider perspective, to identify all cost-effectiveness evaluations of DAAs for the treatment of chronic HCV. For the purposes of this submission, only cost-effectiveness evaluations of drugs relevant to decision-making in England were selected for extraction. The inclusion of these additional, broader search terms does not in any way affect the relevance of the selected studies.

A13. **Priority question:**

a. Please clarify why an economic evaluations limit was applied to the NHS EED search in Appendix 12. This is considered to be too restrictive.

b. Please assess and confirm which records have been lost.

Response

We did not consider this to be overly restrictive since the terms used were broad. Furthermore, as can be seen in Table 9, when looking at records retrieved using the disease area terms alone, no records have been lost.

Table 9: Search strategy for Confirmatory Searches of The Cochrane Library NHS EED (via the Wiley platform) Performed on 30th June 2016 Using the Cost-effectiveness Review Search Strategy

Term group	#	Terms	No. Results
Disease area	#1	[mh "hepatitis c"]	2525
	#2	"hepatitis c" or hcv or "hep c"	6523
	#3	#1 or #2	6523
Economic Evaluations	#4	[mh "health economics"] or [mh "economic evaluation"] or [mh "cost-benefit analysis"] or [mh "cost effectiveness analysis"] or [mh "cost minimization analysis"] or [mh "cost utility analysis"]	24614

Term group	#	Terms	No. Results
	#5	cost* near/2 (effective* or utility* or benefit* or minimi* or consequence*)	35821
	#6	(economic* or pharmacoeconomic*) near/2 (evaluat* or model* or analys?s)	23516
	#7	("quality adjusted life year*" or qaly* or "life year* gained" or "life year* equivalent*" or "incremental cost effective*" or icer)	9513
	#8	#4 or #5 or #6 or #7	42917
Combined	#9	#3 and #8	499
HCV therapies	#10	[mh sofosbuvir] or sofosbuvir or sovaldi* or hepcinat* or hepcvir* or sovihep* or harvoni*	196
	#11	boceprevir or victrelis*	184
	#12	daclatasvir or daklinza*	74
	#13	danoprevir	46
	#14	dasabuvir or exviera*	46
	#15	elbasvir	16
	#16	Grazoprevir or zepatier*	17
	#17	ledipasvir	64
	#18	ombitasvir or viekirax* or paritaprevir or veruprevir or "viekira pak*" or technivie*	52
	#19	[mh simeprevir] or simeprevir or olysio* or galexos* or sovriad*	86
	#20	telaprevir or incivo* or incivek* or telavic*	253
	#21	velpatasvir	10
	#22	"direct acting antiviral*" or DAA*	442
	#23	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	1070
Combined and limits	#24	#9 and #23	52
	#25	#24 in Economic Evaluations	24
	#26	#3 and #23	772
	#27	#26 in Economic Evaluations	24
	#28	**#27 not #25**	**0**

A14. Please provide the search terms and numbers of results for the conference abstract searching reported in Appendix 12.4.

Response

The requested details are provided in Table 10.

Table 10: Search Terms and Numbers of Results for Conference Abstract Searching for the Cost-effectiveness Review

Conference/Database	Search Terms	Results	Unique Relevant Results
European Association for the Study of the Liver (EASL)	Cost-effective Cost effective ICER QALY	14	0
American Association for the Study of Liver Diseases (AASLD) 2015	Cost-effective Cost effective ICER QALY	14	0
American Association for the Study of Liver Diseases (AASLD) 2014	Cost-effective Cost effective ICER QALY	10	0
The Viral Hepatitis Congress 2015	Cost ICER QALY	0	0
The Viral Hepatitis Congress 2014	Cost ICER QALY	1	0
Asian Pacific Association for the Study of the Liver (APASL) 2014	Cost-effective Cost effective ICER QALY	1	0
Asian Pacific Association for the Study of the Liver (APASL) 2015	Cost-effective Cost effective ICER QALY	3	0
Asian Pacific Association for the Study of the Liver (APASL) 2016	Cost-effective Cost effective ICER QALY	13	0
ISPOR (Milan 2015)	Hepatitis C HCV	19	1
ISPOR (Santiago 2015)	Hepatitis C HCV	4	1
ISPOR (Philadelphia 2015)	Hepatitis C HCV	13	0
ISPOR (Amsterdam 2014)	Hepatitis C HCV	22	0
ISPOR (Beijing 2014)	Hepatitis C HCV	5	0
ISPOR (Montreal 2014)	Hepatitis C HCV	8	0

A15. Please provide the search terms and numbers of results for the conference abstract searching reported in Appendix 16.4.

Response

Table 11: Search Terms and Numbers of Results for Conference Abstract Searching for the Measurement and Valuation of Health Effects Review

Conference/Database	Search Terms	Results	Unique Relevant Results
European Association for the Study of the Liver (EASL)	EQ-5D Euroqol	3	1
American Association for the Study of Liver Diseases (AASLD)	EQ-5D Euroqol	4	0
The Viral Hepatitis Congress	EQ-5D Euroqol	1	0

Asian Pacific Association for the Study of the Liver (APASL)	EQ-5D Euroqol	4	2
Interscience Conference on Antimicrobial Agents and Chemotherapy	Hepatitis C HCV	0	0
ISPOR	Hepatitis C HCV	23	0

A16. Please check the date limits applied to the Medline search in Table 25 (Appendix 17.3); specifically the two different date limits applied to lines 44 and 48. Please provide an explanation of the intended outcomes of these limits.

Response

The date limit in line 44 of the strategy for Ovid SP (MEDLINE, MEDLINE In-Process and Embase) was applied to line 43 to allow removal of conference abstracts published at least 2 years ago, in line with the approach to consider conferences from the past 2 years only.

The date limit in line 48 was applied to the whole strategy to limit the results of the strategy to 2011 onwards; cost and resource use data more than 5 years old are likely to have been captured in the previous systematic reviews conducted for the previous submissions for SOF and LDV/SOF (TA330 and TA363).

A17. **Priority question:**

a. Please clarify why a costs/economics limit was applied to the NHS EED search in appendix 17 (Table 26, lines 4-36). This is considered to be overly restrictive.

b. Please assess and confirm which records have been lost.

Response

We did not consider this to be overly restrictive since the terms used were broad and based on the SIGN filter set for economic studies. Furthermore, as can be seen in Table 12, when looking at records retrieved using the disease area terms alone, no records have been lost.

Table 12: Search strategy for Confirmatory Searches of The Cochrane Library NHS EED (via the Wiley platform) Performed on 28th June 2016 Using the Health Resource Identification Review Search Strategy

Term group	#	Terms	No. results
Topic area: chronic HCV	1	[mh "hepatitis C"]	2,525
	2	"hepatitis c" OR hcv OR "hep c"	6,515
	3	#1 OR #2	6,515
Cost and resource use	4	[mh ^economics] or [mh ^socioeconomics] or [mh ^"economic aspect"] or [mh ^"health economics"]	63
	5	[mh ^"costs and cost analysis"]	3848
	6	[mh ^"cost allocation"]	16

Term group	#	Terms	No. results
	7	[mh ^"cost-benefit analysis"] or [mh ^"cost effectiveness analysis"] or [mh ^"cost minimization analysis"]	20997
	8	[mh ^"cost control"]	284
	9	[mh ^"cost savings"]	985
	10	[mh ^"cost of illness"]	1271
	11	[mh ^"cost sharing"]	25
	12	[mh ^"deductibles and coinsurance"]	18
	13	[mh ^"medical savings accounts"]	0
	14	[mh ^"health care costs"] or [mh ^"health care cost"]	4455
	15	[mh ^"direct service costs"]	193
	16	[mh ^"drug costs"]	1741
	17	[mh ^"employer health costs"]	18
	18	[mh ^"hospital costs"] or [mh ^"hospital cost"]	1470
	19	[mh ^"health expenditures"] or [mh ^"health care financing"]	310
	20	[mh ^"capital expenditures"]	6
	21	[mh ^"value of life"]	146
	22	[mh "economics, hospital"]	1731
	23	[mh "economics, medical"]	105
	24	[mh ^"economics, nursing"]	19
	25	[mh ^"economics, pharmaceutical"]	243
	26	[mh "fees and charges"]	502
	27	[mh "budgets"] or [mh ^"financial management"]	89
	28	low next cost	2146
	29	high next cost	805
	30	(health care or healthcare or health-care) next cost*	8103
	31	fiscal or funding or financial or finance	29913
	32	cost next estimat*	3349
	33	cost next variable	8
	34	unit next cost*	5190
	35	economic* or pharmacoeconomic* or price* or pricing	41931
	36	(resource* or healthcare* or service*) near/3 (use* or utilis* OR utiliz* or consume* or consuming or consumption*)	15404
	37	{or #4(1-#36)	67872
Combined and limits	38	#3 and #37	751
	39	#3 not #37	5764
		#38 in Economic Evaluations (NHS EED)	259
		#39 in Economic Evaluations (NHS EED)	0
		#38 Publication Year from 2011 to 2016, in Economic Evaluations (NHS EED)	81
		#39 Publication Year from 2011 to 2016, in Economic Evaluations (NHS EED)	0

Section B: Clarification on effectiveness data

B1. **Priority question:** Please provide the data that was used in each WinBUGS MTC model in the WinBUGS format (ideally as an Excel spreadsheet).

Response

The requested Excel data has been provided separately via NICE Docs.

B2. **Priority question:** Table 39 provides the sources for the SVR inputs in the economic model. However, the company have selected one study for each SVR, even when multiple sources are available, and in some cases, the justification does not seem appropriate.

a. Please provide a meta-analysis (using a standard method such as inverse variance) of SVR and safety rates (i.e. treatment-related adverse events), one for each treatment in each subgroup using all sources of data available.

Response

As noted in Table 39 of the company submission, for the majority of treatments in each subgroup, only one relevant data source for SVR rate was available and therefore a meta-analysis was not possible (these are indicated with N/A).

For those treatments with more than one possible source of SVR rate in specific patient subgroups, the justification for using the chosen source is provided Table 39. However, additional explanation is provided in response to this clarification question, either in the tables below or in response to B2 parts b-d.

Table 13: SVR sources for SOF+RBV in GT3 TN

Patient Subgroup	Treatment	Source of SVR rate	Alternative source of SVR rate
GT3 TN (NC and CC)	SOF+RBV 24w	ASTRAL-3 trial	BOSON; VALENCE; ELECTRON

The rationale for use of the ASTRAL-3 trial and the impact of using the SVR rate from BOSON is explored in response to B.2 part b (i). Neither the VALENCE trial nor the ELECTRON trial were considered appropriate sources of SVR rate for SOF+RBV 24w. As discussed in Section 4.10.8 of the company submission, VALENCE was initially designed to

compare SOF+RBV 12 weeks with placebo in patients with HCV GT2 or GT3 infection. However, emerging data from the Phase III FUSION trial indicated that patients with HCV GT3 infection had higher response rates when treated for 16 weeks compared with 12 weeks. As a result the VALENCE trial was unblinded, and treatment for all patients with HCV GT3 infection was extended to 24 weeks and the placebo group terminated. The trial was redefined as a descriptive study to characterise SVR rates in patients with HCV GT2 infection treated for 12 weeks, and in patients with HCV GT3 infection treated for 24 weeks, with no plans for hypothesis testing. For this reason, the VALENCE trial did not fulfil the criteria for inclusion in the systematic literature review described in Section 4.1 of the company submission and was considered unsuitable for use as a source of SVR rate in the economic model.

Regarding the ELECTRON trial, it is an error in the company submission to state that this small Phase II trial is an alternative source of SVR rate for SOF+RBV 24w, as this treatment regimen was not tested in ELECTRON. Our apologies for this error.

Table 14: SVR sources for SOF+Peg-IFN+RBV 12w in GT3 TN

Patient Subgroup	Treatment	Source of SVR rate	Alternative source of SVR rate
GT3 TN (NC and CC)	SOF+Peg-IFN+RBV 12w	BOSON	ELECTRON; PROTON; LONESTAR-2

As described in Table 39 of the company submission, the BOSON trial data were considered most appropriate for this SVR rate due to the large size of this dataset, the fact that it was a Phase III randomised trial and that it reported SVR rates for SOF+Peg-IFN+RBV 12w in each GT3 patient population included in the NICE scope (i.e. the data were split as required within the NICE scope, with separate reporting of cirrhotic / non-cirrhotic outcomes). Aside from the small LONESTAR-2 PhII trial (n=22), it is the only available trial which does present SVR rates stratified by cirrhosis status. In addition, the BOSON trial involved participation from 25 clinical trial centres in the United Kingdom.

In relation to the ELECTRON, PROTON or LONESTAR-2 trials, the Summary of Product Characteristics for sofosbuvir states:

"These are exploratory or Phase 2 studies. The outcomes should be interpreted with caution, as subject numbers are small and SVR rates may be impacted by the selection of patients. In the ELECTRON study (N = 11), the duration of peginterferon alfa ranged from 4-12 weeks in combination with sofosbuvir + ribavirin."

For this reason, the ELECTRON, PROTON and LONESTAR-2 trials were considered unsuitable given that the Phase III BOSON trial data were available.

Table 15: SVR sources for SOF+RBV in GT3 TE

Patient Subgroup	Treatment	Source of SVR rate	Alternative source of SVR rate
GT3 TE (NC and CC)	SOF+RBV 24w	ASTRAL-3	VALENCE

As described in Table 39 of the submission, the ASTRAL-3 trial is the largest Phase III dataset for SOF+RBV in GT3 patients and allows a head to head comparison to be made with SOF/VEL; as such it is considered more appropriate than the VALENCE trial, even considering the issues described above regarding the robustness of the VALENCE data.

Table 16: SVR sources for OBV/PTV/RTV+DSV+RBV 12w in GT1 TN

Patient Subgroup	Treatment	Source of SVR rate	Alternative source of SVR rate
GT1 TN (NC and CC)	OBV/PTV/RTV+DSV+RBV 12w (GT1a NC)	PEARL-IV	SAPPHIRE-I

As described in Table 39 of the submission, PEARL-IV and SAPPHIRE-I were comparable studies, which both included UK patients. SVR rates were almost identical in both trials. The SVR rate for this regimen from the Phase III PEARL-IV study that was used in the economic model was 97.0%. In the Phase III trial, SAPPHIRE-I trial, the corresponding SVR rate was 96.0%. Therefore a conservative approach was taken in the original STA, incorporating the higher SVR; given that the SVR rates are virtually identical, performance of a meta-analysis is considered not to be informative.

Table 17: SVR sources for Peg-IFN+RBV 48w in GT1 TN

Patient Subgroup	Treatment	Source of SVR rate	Alternative source of SVR rate
GT1 TN (NC and CC)	Peg-IFN+RBV 48w	IDEAL (McHutchison et al, 2009)	McHutchison is a large dataset and allows treatment outcomes on Peg-IFN+RBV in GT1 TN patients to be stratified by cirrhosis status

As described in Table 39 of the submission, the IDEAL trial is considered the most appropriate source of SVR rate for Peg-IFN+RBV 48w in GT1 TN (NC and CC) patients. This approach was previously deemed acceptable by the NICE Appraisal Committee (TA330), where the conclusion was as follows:

"On balance, the Committee concluded that the sustained virological responses from McHutchison et al. were an acceptable source for including in its base-case model, but noted that the sustained virological responses could lie between those provided by the McHutchison and Hadziyannis data sets."

The Hadziyannis (2) dataset was identified by the ERG for TA330 as a potentially relevant alternative source for the SVR rate for Peg-IFN+RBV 48w in GT1 TN (NC and CC) patients, in which the SVR rates were 56% and 38%, respectively as compared to SVR rates of

43.6% and 23.6% for GT1 TN NC and CC patients respectively from the McHutchison dataset.

A scenario analysis has been conducted by using the Hadziyannis dataset in GT1 TN (NC and CC). The results are presented in Table 18 and Table 19.

Table 18: GT1 treatment-naïve non-cirrhotic (anticipated list price). Hadziyannis SVR data for PegIFN+RBV (48w)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£16,304	18.97	13.63					
PegIFN + RBV (48 wks)	£19,002	20.70	15.66	£2,698	1.73	2.03	£1,329	£1,329
Ledipasvir/sofosbuvir (8 wks)	£29,713	21.73	17.10	£13,409	2.76	3.47	£3,868	£7,438
Simeprevir + PegIFN + RBV (RGT)	£33,817	21.40	16.61	£17,512	2.43	2.97	£5,890	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£41,331	21.67	16.98	£25,027	2.69	3.35	£7,471	Dominated
Sofosbuvir/velpatasvir (12 wks)	£41,829	21.86	17.27	£25,525	2.89	3.63	£7,028	£73,604
Sofosbuvir + daclatasvir (12 wks)	£62,383	21.91	17.32	£46,079	2.94	3.69	£12,486	£349,606

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

Table 19: Base-case results: GT1 treatment-naïve cirrhotic (anticipated list price). Hadziyannis SVR data for PegIFN+RBV (48w)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
PegIFN + RBV (48 wks)	£41,128	12.80	7.08	£5,337	3.44	2.11	£2,534	£2,534
Simeprevir + PegIFN + RBV (RGT)	£55,825	14.40	8.16	£20,035	5.04	3.18	£6,299	Ext. Dominated
Sofosbuvir/velpatasvir (12 wks)	£59,495	17.34	10.11	£23,705	7.98	5.13	£4,620	£6,062
Ledipasvir/sofosbuvir (12 wks)	£60,349	16.98	9.88	£24,559	7.63	4.90	£5,009	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£61,014	15.91	9.16	£25,224	6.56	4.19	£6,021	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

Table 20: SVR sources for Peg-IFN+RBV 48w in GT1 TE

Patient Subgroup	Treatment	Source of SVR rate	Alternative source of SVR rate
GT1 TE (NC and CC)	Peg-IFN+RBV 48w	REALIZE (Study C216) (TVR SmPC and Zeuzem 2011)	REALIZE trial allows stratification of treatment outcomes on Peg-IFN+RBV in GT1 TE patients by cirrhosis status

In GT1 TE patients treated with Peg-IFN+RBV 48w, the most relevant dataset is the REALIZE trial, which compared TPV+Peg-IFN+RBV versus Peg-IFN+RBV 48w. This dataset was used in the NICE appraisal of telaprevir (TA252) as well as in the Gilead SOF and LDV/SOF NICE appraisals (TA330 and TA 363 respectively), where the dataset was accepted as representative in the basecase by respective Appraisal Committees.

In relation to safety (AE) rates, a similar approach has been taken in the company submission of selecting what is considered to represent the most appropriate source of data for each treatment in the model. A meta-analysis of safety rates has therefore not been performed. Upon reviewing the output of deterministic sensitivity analyses presented in the company submission, it is clear that the extremely low AE rates associated with DAA treatment over a very short time period in the model has little meaningful impact on the cost-effectiveness results. It is therefore considered justifiable to continue with the approach taken in the company submission. It should be noted that this approach mirrors the approach that was previously accepted by NICE in the Gilead SOF and LDV/SOF appraisals (TA330 and TA363).

b. Please provide further justification why certain studies were selected and not others.

    i. For instance, under ‘GT3 TN (NC and CC)’, second row: SOF+RBV 24w, ASTRAL-3 was chosen because it has a head-to-head comparison with SOF/VEL 12w; however, BOSON has a head-to-head comparison with SOF+Peg-INF+RBV 12w which is also in the network and would therefore be just as appropriate; please explain why BOSON was not chosen.

Response

The ASTRAL-3 trial is considered the most appropriate source of SVR rate for SOF+RBV 24w in GT3 given that it has been studied in a large Phase III randomised trial versus the intervention being appraised (i.e. SOF/VEL 12w). Nevertheless, it is acknowledged that the BOSON trial could also have been a reasonable source for this SVR rate. To explore the impact of this, a scenario analysis has been conducted in which the BOSON trial data are used for the SVR rate of SOF+RBV 24 rather than the ASTRAL-3 trial data. The results are presented in Table 21 and Table 22. This shows that the cost-effectiveness results remain

unchanged regardless of whether ASTRAL-3 or BOSON is used to provide an SVR rate for SOF+RBV 24w (i.e. SOF+RBV 24w remains dominated).

ii. Similarly, for SOF+DCV 12w (page 132), ALLY-3 was chosen, but it is not clear why AI444040 would not be equally appropriate.

Response

Only the 12w SOF+DCV regimen is recommended by NICE for F3/F4 patients with genotype 3. The ALLY-3 trial provided SOF+DCV 12w data for CHC genotype 3 F3/F4 patients, which is aligned with the NICE Guidance in TA365. The CHC genotype 3 patients included in the AI444040 trial were treated with a 24w regimen of SOF+DCV (+ RBV), and therefore this trial does not provide data for SOF+DCV 12w in F3/F4 patients. It should also be noted that ALLY-3 is also a much larger trial that the AI444040 trial (in treatment-naïve patients, n=148 for ALLY-3 versus n=13 for AI444040; in treatment-experienced patients, n=155 versus n=5 for AI444040) and ALLY-3 was a trial conducted specifically in the CHC genotype 3 population whereas AI444040 was not. For these reasons the ALLY-3 trial is the most appropriate data source for this SVR input and a scenario analysis using the AI444040 trial was not conducted.

c. For SOF+DCV+RBV 24w (page 132) there are no data, so data for SOF+DCV 12w from ALLY3 are used. Please confirm that the company searched for all possible study types including case series, for evidence for SOF+DCV+RBV 24w?

Response

As described in response to part ii, a small number of patients with CHC genotype 3 (treatment-naïve only, n=5) in the AI444040 trial were treated with a 24w regimen of SOF+DCV+RBV. The SVR rate was 100%.This study was identified in the systematic review of clinical effectiveness described in Section 4.1 of the company submission and it is therefore an error in Table 39 to state that there are no data available for this treatment regimen, Please accept our apologies for this oversight. There are also limited, non-randomised data available with this regimen from the French Compassionate Use Programme, which was not identified in the systematic review of clinical effectiveness studies described in Section 4.1 of the company submission given that it is not a randomised controlled trial. The available data from the Compassionate Use Programme (N=53) does not stratify SVR rates by treatment history *and* cirrhosis status, in line with the NICE scope (i.e. data are available by treatment history and cirrhosis status, separately)

In this Compassionate Use Programme, the SVR12 rate with SOF+DCV+RBV 24w was 100% and 86% in patients without and with cirrhosis, respectively, and 82% and 80% in treatment-naïve and treatment-experienced patients, respectively.

Given that the 24w regimen of SOF+DCV+RBV is only recommended by NICE for GT3 cirrhotic patients who are interferon-ineligible, scenario analyses have been performed to

explore the impact of using the SOF+DCV+RBV 24w data from the French CUP to provide SVR rates for GT3 TN CC and TE CC patients in the economic model.

SVR rates of 100% and 86% for GT3 TN CC and TE CC, respectively have been used, in order to be consistent with the small dataset available from the AI444040 trial, in which the SVR rate for SOF+DCV+RBV 24w in GT3 TN CC patients was also 100%). The results are presented in Table 21 and Table 22. The overall cost-effectiveness results remain unchanged (i.e. SOF+DCV+RBV 24w remains dominated or is not cost-effective).

Table 21: GT3 treatment-naive cirrhotic IFN-ineligible (anticipated list price): SOF+RBV(24wk) with BOSON SVR data, SOF+DCV+RBV(24w) with French CUP SVR data (was Table 134 in company submission)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,790	9.36	4.98					
Sofosbuvir/velpatasvir (12 wks)	£60,544	16.89	9.82	£24,754	7.54	4.85	£5,107	£5,107
Sofosbuvir + daclatasvir + RBV (24 wks)	£80,951	17.45	10.17	£45,161	8.09	5.19	£8,702	£58,306
Sofosbuvir + RBV (24 wks)	£95,743	16.10	9.29	£59,953	6.74	4.31	£13,910	Dominated

Table 22: GT3 treatment-experienced cirrhotic IFN-ineligible (anticipated list price): SOF+RBV(24wk) with BOSON SVR data, SOF+DCV+RBV(24w) with French CUP SVR data (was Table 136 in company submission)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£35,361	9.27	4.93					
Sofosbuvir/velpatasvir (12 wks)	£59,612	15.96	9.26	£24,251	6.69	4.33	£5,599	£5,599
Sofosbuvir + daclatasvir + RBV (24 wks)	£81,705	15.72	9.10	£46,344	6.45	4.17	£11,114	Dominated
Sofosbuvir + RBV (24 wks)	£95,051	15.15	8.70	£59,690	5.88	3.77	£15,833	Dominated

d. For Peg-IFN+RBV 24w (page 132), there is a rational presented for using FISSION. However, this rational suggests that there might be other relevant sources.

    i. Please clarify which other relevant sources there are.

Response

A number of trials of Peg-IFN+RBV for the treatment of GT3 treatment-naïve patients have been identified in the systematic review of clinical effectiveness described in Section 4.1 of the company submission. Probabilities of SVR for pegylated interferon + ribavirin (Peg+RBV) in treating genotype 3, treatment-naïve chronic hepatitis C (HCV) have been synthesised using the inverse variance approach (3). Safety was not analysed due to insufficient data. Three analyses have been presented:

1. Evidence synthesised from studies included in the genotype 3, treatment-naïve network (based on the systematic literature review (SLR) of randomised controlled trials (RCTs)) (Section 4.10 of the submission).
2. Evidence synthesised from all studies identified by the SLR of RCTs for genotype 3, treatment-naïve patients (Section 4 of the submission). This included studies identified by the SLR which compared pegylated-interferon regimens only (appendix 6 of the submission)
    a. All patients
    b. Cirrhotic patients (metavir score F4)
    c. Non-cirrhotic patients (metavir score F0-F3)
3. Evidence synthesised from all Peg24+RBV24 studies identified by the SLR of RCTs for genotype 3, treatment-naïve patients (Section 4 of the submission). This included studies identified by the SLR which compared pegylated-interferon regimens only (appendix 6 of the submission)

The inverse variance approach was applied as follows:

$$SVR = \frac{\sum_i SVR_i . w_i}{\sum_i w_i}$$

Where $SVRi$ denotes SVR in study i and Wi denotes the weight given to study i. The weight of a study is given by:

$$Wi = \frac{1}{se_i^2}$$

Where se_i is the standard error of the probability of SVR in study i. This was computed using the following formula:

$$se_i = \sqrt{\frac{SVR_i * (1 - SVR_i)}{N_i}}$$

Input data for analysis 1 are presented in Table 23. Synthesising these data using the inverse variance method generates a probability of SVR of 0.60.

Table 23: Input data for SVR – only studies included in network for genotype 3, treatment naïve HCV

Study	Treatment	N	n	%	s.e.
AI444-031	PBO+Pega24+RBV24	27	14	51.9	0.10
FISSION	Peg24+RBV24	176	110	62.5	0.04
Foster 2011	PBO+Peg24+RBV24	9	4	44	0.17

Input data for analysis 2a are presented in Table 24. Synthesising these data using the inverse variance method generates a probability of SVR of 0.65.

Table 24: Input data for SVR – all studies identified by the SLR of RCTs for genotype 3, treatment naïve HCV – all patients

Study	Treatment	N	n	%	s.e.
AI444-031	PBO+Pega24+RBV24	27	14	51.9	0.10
FISSION	Peg24+RBV24	176	110	62.5	0.04
Foster 2011	PBO+Peg24+RBV24	9	4	44	0.17
Mangia 2010	Peg2b24+RBV24	207	148	71.5	0.03
Mangia 2010	Peg2b12/36+RBV12/36	207	154	74.9	0.03
Ascione 2010	Peg2a12+RBV12	18	14	77.8	0.10
Ascione 2010	Peg2b12+RBV12	17	12	70.6	0.11
NORDynamIC	Peg2a12+RBV12	137	79	58	0.04
NORDynamIC	Peg2a24+RBV24	139	108	78	0.04
Rumi 2010	Peg2a24+RBV24	34	22	65	0.08
Rumi 2010	Peg2b24+RBV24	32	22	69	0.08
ACCELERATE	Peg2a16+RBV16	358	222	62	0.03
ACCELERATE	Peg2a24+RBV24	369	244	66	0.02
Manns 2011	Peg2b24+RBV24	192	124	65	0.03
Manns 2011	Peg2b16+RBV16	180	99	55	0.04
STEPS	Peg24+RBV24	67	32	48	0.06
STEPS	Peg48+RBV48	69	29	42	0.06

Input data for analysis 2b are presented in Table 25. Synthesising these data using the inverse variance method generates a probability of SVR of 0.43.

Table 25: Input data for SVR – all studies identified by the SLR of RCTs for genotype 3, treatment naïve HCV – cirrhotic patients (metavir score F4)

Study	Treatment	N	n	%	s.e.
AI444-031	PBO+Pega24+RBV24	7	-	43	0.19
STEPS	Peg24+RBV24	41	19	46	0.08
STEPS	Peg48+RBV48	43	17	40	0.07

Input data for analysis 2c are presented in Table 26. Synthesising these data using the inverse variance method generates a probability of SVR of 0.59.

Table 26: Input data for SVR – all studies identified by the SLR of RCTs for genotype 3, treatment naïve HCV – non-cirrhotic patients (metavir score F0-F3)

Study	Treatment	N	n	%	s.e.
AI444-031	PBO+Pega24+RBV24	20	-	65	0.11
Foster 2011	PBO+Peg24+RBV24	9	4	44	0.17

Input data for analysis 3 are presented in Table 27. Synthesising these data using the inverse variance method generates a probability of SVR of 0.67.

Table 27: Input data for SVR – Peg24+RBV24 studies identified by the SLR of RCTs for genotype 3, treatment naïve HCV

Study	Treatment	N	n	%	s.e.
AI444-031	PBO+Pega24+RBV24	27	14	51.9	0.10
FISSION	Peg24+RBV24	176	110	62.5	0.04
Foster 2011	PBO+Peg24+RBV24	9	4	44	0.17
Mangia 2010	Peg2b24+RBV24	207	148	71.5	0.03
NORDynamIC	Peg2a24+RBV24	139	108	78	0.04
Rumi 2010	Peg2a24+RBV24	34	22	65	0.08
Rumi 2010	Peg2b24+RBV24	32	22	69	0.08
ACCELERATE	Peg2a24+RBV24	369	244	66	0.02
Manns 2011	Peg2b24+RBV24	192	124	65	0.03
STEPS	Peg24+RBV24	67	32	48	0.06

In the FISSION trial, and as used in the economic model, the SVR rate with Peg-IFN+RBV 24w was 71.2% in GT3 TN NC patients. The GT3 meta-analyses outlined above indicate that the pooled estimates of SVR rate for Peg-IFN+RBV range from 59% to 67%. Therefore, use of the FISSION trial may even be a conservative approach, given the results of the meta-analyses presented above, and in the context of the real-world effectiveness of Peg-IFN+RBV 24w in GT3 patients described in the company submission , which show that the efficacy of Peg-IFN+RBV 24w in a large UK treatment centre ranged from 60% - 68% approximately (4).

ii. And please clarify in general whether all possible sources for each treatment/population have been listed (including all study types) in Table 39.

Response

As described in response to parts b-d of this clarification question, for the majority of treatments in the economic model, only one data source for SVR rate was available.

For those treatments where more than one data source for SVR rate was available, the choice of trial to provide SVR rate in the economic model has been justified, either in the original company submission or in response to this clarification question.

In relation to Peg-IFN+RBV 24w in GT3 TN patients, as described in part d, a number of trials have been identified in the context of systematic literature review. A meta-analysis has been conducted of these trials with results indicating that the approach taken in the company submission of using the FISSION trial as a source of SVR rate is appropriate. In relation to Peg-IFN+RBV 48w in GT1 patients, again a number of potentially relevant trials have been identified in the context of systematic literature review.

These trials (for GT1 TN and GT1 TE patients) are presented below. A formal meta-analysis of these trials has not been conducted as it is considered that the approach taken in the company submission of using the SVR rates from the IDEAL trial and the REALIZE trial for GT1 TN and GT1 TE patients respectively, has been adequately justified in response to part a of this clarification question. Also, visual inspection of the results of the trials presented in Table 28 and Table 29 indicates the trial-specific estimates of the SVR rate for Peg-IFN+RBV 48w in GT1 patients from the IDEAL and REALIZE trials are generally in line with the range of estimates from the available literature. The exception to this is the results of the PhIII PROMISE trial, in which the SVR rates on Peg-IFN+RBV 48w in GT1 TE patients were 38% and 26% in NC and CC patients, respectively (see Table 29). However, scenario analyses have been conducted to explore the impact of using the PROMISE trial data rather than the REALIZE trial data and the results (not presented here) show that the overall cost-effectiveness conclusions as presented in the company submission for this patient population remain unchanged.

Therefore, in general it is confirmed that all possible sources for each treatment/population in the model have either been listed in the company submission or that the approach taken in the company submission to selection of SVR rate for particular treatments has been justified in this clarification question response.

Studies which report SVR for Peg+RBV in genotype 1, treatment-naïve and treatment-experienced chronic Hepatitis C patients are presented in Tables 28 and 29.

Table 28: Genotype 1, treatment-naïve, Peg+RBV studies

StudyID	Treatment	TN/TE	Genotype	Metavir score	N	n	%	Cirrhotic (F4) SVR (%)	Non-cirrhotic (F0-F3) SVR (%)
QUEST-2	PBO12+Peg24/48+RBV24/48	TN	1	F0-F4	134	67	50	40	51
COMMAND-1	PBO24+Peg2a48+RBV48	TN	1	-	72	26	36.1	38	-
QUEST-1	PBO12+Pega12+RBV12+Pega36+RBV36	TN	1	F0-F4	130	65	50	29	53
PROVE 2	Peg48+RBV48	TN	1	F0-F3	82	38	46.3	-	46.3
ADVANCE	Peg48+RBV48	TN	1	F0-F4	361	158	43.8	33	47
SPRINT-1	Peg48+RBV48	TN	1	F0-F3	104	39	37.5	-	37.5
SPRINT-2	PBO44+Peg48+RBV48	TN	1	F0-F3	363	137	37.7	-	37.7
PILLAR	PBO+Peg48+RBV48	TN	1	F0-F3	77	51	66.2	-	66.2
Lawitz 2013	PBO12+Peg48+RBV48	TN	1	F0-F3	26	15	58	-	58
PROVE1	PBO12+Peg48+RBV48	TN	1	F0-F3	75	-	41	-	41
Pol 2012	Peg48+RBV48	TN	1	F0-F3	12	-	25	-	25
Rodriguez-Torres 2013	PBO4+Peg48+RBV48	TN	1	F0-F3	14	7	50	-	50
Buti 2010	PegIFN2b48+RBV48	TN	1	-	86	-	43	-	-
Buti 2010	PegIFN2b72+RBV72	TN	1	-	73	-	48	-	-
Berak 2014	PegIFN2a48+RBV48	TN	1	F0-F4	101	50	49.5	-*	54.1
Berak 2014	PegIFN2b48+RBV48	TN	1	F0-F4	111	49	44.1	-*	50.6
Berg 2006	Pega48+RBV48	TN	1	F0-F4	230	121	53	-	-
Berg 2006	Pega72+RBV72	TN	1	F0-F4	225	121	54	-	-
IDEAL	Peg2b48+RBV48	TN	1	F0-F4	1019	406	39.8	-*	42.1
IDEAL	Peg2a48+RBV48	TN	1	F0-F4	1035	423	40.9	-*	43.6
Pearlman 2007	Peg2b48+RBV48	TN	1	-	49	-	18	-	-
Pearlman 2007	Peg2b72+RBV72	TN	1	-	52	-	38	-	-
Rumi 2010	Peg2a48+RBV48	TN	1	-	91	44	48	-	-
Rumi 2010	Peg2b48+RBV48	TN	1	-	87	28	32	-	-
Pegasus	Peg2a24+RBV24	TN	1	F0-F3	32	6	19	-	19

StudyID	Treatment	TN/TE	Genotype	Metavir score	N	n	%	Cirrhotic (F4) SVR (%)	Non-cirrhotic (F0-F3) SVR (%)
Brazilian Study									
Pegasus Brazilian Study	Peg2a48+RBV48	TN	1	F0-F3	31	15	48	-	48
Yenice 2006	Peg2a24/24+RBV24/24	TN	1	-	37	-	48.6	-	-
Yenice 2006	Peg2b24/24+RBV24/24	TN	1	-	37	-	35.1	-	-

*Only reports SVR for F3-F4 and not F4 exclusively

Table 29: Genotype 1, treatment-experienced, Peg+RBV studies

StudyID	Treatment	TN/TE	Genotype	Metavir score	N	n	%	Cirrhotic (F4) SVR (%)	Non-cirrhotic (F0-F3) SVR (%)
Flamm 2013	PBO44+PegIFNa48+RBV48	TE	1	F0-F4	67	14	21	-*	21
REALIZE	PBO16+PegIFN2a48+RBV48	TE	1	F0-F4	132	22	17	-*	-
PROVE3	PBO24+PegIFN2a48+RBV48	TE	1	F0-F4	114	16	14	8	15
ASPIRE	PBO48+PegIFN2a48+RBV48	TE	1	F0-F4	66	15	22.7	-	-
RESPOND-2	PBO44+PegIFN2b48+RBV48	TE	1	F0-F4	80	17	21	-*	24
PROMISE	PBO12+PegIFN2a48+RBV48	TE	1	F0-F4	133	48	36.1	26	38
PHOENIX	Peg2a48+RBV48	TE	1	-	43	-	18.6	-	-
Scotto 2008	Peg2a12/36+RBV12/36	TE	1	F0-F4	45	8	17.8	-	-
Scotto 2008	Peg2b12/36+RBV12/36	TE	1	F0-F4	47	6	12.8	-	-

*Only reports SVR for F3-F4 and not F4 exclusively

e. For Peg-IFN+RBV 24w in GT3 TE (NC and CC) (page 131), these data should correspond with the same intervention in Table 94, page 232. However, in Table 94, Peg-IFN+RBV 48w is listed.

i. Please clarify this discrepancy in the treatment duration?

Response

This is a typo; in Table 94 it should read “Peg-IFN+RBV 24w”. Please accept our apologies.

ii. Please clarify what is meant by ‘accepted’ in the sentence “Accepted previously in NICE TA330 for SOF” (page 131). Please confirm whether NICE specifically agreed that this was acceptable?

Response

These data were used to derive the SVR rate for this treatment in basecase analysis in TA330 (given that these data were the best available at that time). This approach for the TA330 basecase was not specifically criticised or stated to be incorrect by NICE during the appraisal process. No suitable alternative source of data has become available since TA330 (nor is any additional data likely to become available in the future given that interferon-based treatments are rapidly becoming obsolete in CHC (and specifically, retreatment with IFN/RBV, without addition of a DAA, in a patient with prior failure to the same regimen)). It is therefore considered appropriate to use the same data (and derived SVR rate) for this patient subgroup in the current appraisal.

Section C: Clarification on cost-effectiveness data

Cost effectiveness review

C1. Details and results of the following studies have not been extracted in the cost effectiveness review performed in the company submission. It is not clear why these studies were not extracted. In particular, the rationale: 'Does not include DAA regimens of particular interest' does not seem valid when applied to studies with appropriate comparators (for example, Cure et al, 2014, which studied telaprevir in combination with pegylated interferon alpha and ribavirin in previously untreated chronic hepatitis C genotype 1 patients). Please extract data from the following studies as performed in Table 15 of Appendix 12.

a. Cure S, Bianic F, Gavart S, et al. Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in previously untreated chronic hepatitis C genotype 1 patients. Journal of Medical Economics 2014;17:65-76.

b. Cure S, Bianic F, Gavart S, et al. Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in treatment-experienced chronic hepatitis C genotype 1 patients. Journal of Medical Economics 2014;17:77-87.

c. Westerhout K, Treur M, Mehnert A, et al. A cost utility analysis of simeprevir used with peginterferon + ribavirin in the management of genotype 1 hepatitis C virus infection, from the perspective of the UK National Health Service. Journal of Medical Economics 2015;18:838-849.

d. National Institute for Health and Care Excellence (NICE). Sofosbuvir for treating chronic hepatitis C (TA330). 2015.

e. National Institute for Health and Care Excellence (NICE). Boceprevir for the treatment of genotype 1 chronic hepatitis C (TA253). 2012.

f. National Institute for Health and Care Excellence (NICE). Telaprevir for the treatment of genotype 1 chronic hepatitis C (TA252). 2012.

g. National Institute for Health and Care Excellence (NICE). Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C (TA331). 2015.

Response

The NICE user guide for manufacturers' submissions specifies that a brief overview of each cost-effectiveness study should be provided "only if it is relevant to decision-making in England". Given the rapid advances in the HCV treatment landscape and the availability of comprehensive recent cost-effectiveness evaluations, the publications selected for extraction were judged to provide the most relevant results for decision-making in England at the present time (in particular exclusion of telaprevir in line with agreement from the Decision Problem meeting on 24/04/2016).

Cost-effectiveness evaluations were originally extracted where they presented analyses including the newest generation of DAAs with high cure rates (i.e. regimens containing

sofosbuvir, daclatasvir or ombitasvir), as these regimens are the most comparable to sofosbuvir/velpatasvir. These included several studies comparing the newer DAA regimens to appropriate older regimens (ie. regimens containing telaprevir or boceprevir); for example:

- Cure 2015 which included comparisons to telaprevir- and boceprevir-based regimens
- McEwan 2016, NICE TA363, NICE TA364 and NICE TA365 which included comparisons to telaprevir-, boceprevir- and simeprevir-based regimens.

Given that simeprevir is a comparator in the model, we agree that these data may also be useful for comparison. However, telaprevir and boceprevir are not included as comparators in the model presented in the submission (as discussed and agreed at the NICE Decision Problem meeting for this appraisal on 24/04/2016 and outlined in Table 1 of the company submission). Therefore, additional extractions and quality assessments for publications relating to simeprevir (NICE TA331 and Westerhout 2015) have been performed and these are provided in Table 30 and Table 31 below.

NICE TA330 (Sofosbuvir for treating chronic hepatitis C) was also identified in the SLR and is included on the list suggested by the ERG for additional data extraction. Although sofosbuvir-based regimens were of interest, NICE TA330 (Sofosbuvir for treating chronic hepatitis C) was followed by NICE TA363 (Ledipasvir–sofosbuvir for treating chronic hepatitis C). The model presented in TA363 included earlier sofosbuvir-based regimens (sofosbuvir + peg-interferon/ribavirin, sofosbuvir + simeprevir), and therefore provides more recent and relevant results for decision-making.

Therefore, in line with the above, extraction of the two publications relating to simeprevir, have been performed and are provided below.

Table 30: Additional Extractions for Simeprevir Studies Identified in the Cost-effectiveness Review

<table>
<tr><th>Author (Year) [Cost Year]</th><th>Summary of model: Analysis or Model Type; Analysis Time Frame; and Rationale for Design and Time Frame</th><th>Patient Population, including Average Age</th><th>Interventions & Comparators, and Sequences of Treatments in the Model, if Applicable</th><th>Cost</th><th>Outcome</th><th>ICER</th></tr>
<tr><td>NICE TA331 2014 [2012]</td><td>The model that has been developed for this submission is based on published models that have been used in previous NICE single technology appraisals (TA252 and TA253).

A state transition Markov model was used to produce a cost-effectiveness analysis.

The model is composed of two phases. The first - the ‘treatment’ phase - relates to the initial anti-viral treatment period. This phase includes up to 48 weeks of treatment followed up to a 24 week post treatment period, at which point the viral response is assessed. Based on the outcome, patients then move into the ‘post treatment’ Markov phase of the model, which captures long term outcomes over the remaining life of the patient. The health states a patient can be in include: Mild HCV (F0-F2), Moderate HCV (F3) compensated cirrhosis (F4), with an SVR version of these health states as well as decompensated cirrhosis, Hepatocellular carcinoma, Liver transplant, post liver transplant and death.</td><td>Adults with genotype 1 or 4 chronic hepatitis C both treatment naïve and treatment experienced (prior relapsers, and partial and null responders)

Patients baseline characteristics:
• Age 50.0 years
• 71.2% male
• 79.0kg weight

Baseline disease severity (treatment naïve):
• 45.0% F0-F2
• 35.0% F3
• 20.0% F4

Baseline disease severity (treatment experienced):
• 25.0% F0-F2
• 45.0% F3
• 30.0% F4

Genotype 1a patients with the</td><td colspan="3">SMV/PR - SMV/PR 12 weeks + 12 further weeks PR
TVR/PR - TVR/PR 12 weeks + 36 weeks PR only
BOC/PR - PR alone for 4 weeks then BOC/PR further 32 weeks then PR for further 12 weeks
PR - PR alone for 48 weeks
SMV/SOF - SMV/SOF for 12 weeks

Base case results for SMV/PR vs comparators (discounted) are presented below. Undiscounted results for costs and QALYs were presented but not extracted. Cost/QALY/ICER tables for each comparator vs PEG-IFN and cost effectiveness frontier tables were also reported for GT1 patients but not extracted.</td><td></td></tr>
</table>

Population	Treatment	Cost	Incremental cost SMV/PR vs comparator	QALY	Incremental QALY SMV/PR vs comparator	ICER SMV/PR vs comparator
Treatment naïve GT1	**SMV/PR**	£36,778	-	12.390	-	-
	TVR/PR	£40,945	-£4,167	12.275	0.114	Dominant
	BOC/PR	£38,898	-£2,119	12.242	0.147	Dominant
	PR	£26,316	£10,463	11.653	0.736	£14,206
Treatment experienced GT1	**SMV/PR**	£43,544	-	11.258	-	-
	TVR/PR	£44,502	-£958	11.226	0.032	Dominant
	BOC/PR	£49,582	-£6,038	11.128	0.130	Dominant
	PR	£34,424	£9,120	10.327	0.931	£9,793
Treatment naïve GT4	**PR**	£26,836	£8,802	12.274	0.755	£11,662
	SMV/PR	£35,638	-	13.029	-	

<table>
<tr><th>Author (Year) [Cost Year]</th><th>Summary of model: Analysis or Model Type; Analysis Time Frame; and Rationale for Design and Time Frame</th><th>Patient Population, including Average Age</th><th colspan="7">Interventions & Comparators, and Sequences of Treatments in the Model, if Applicable</th></tr>
<tr><td></td><td>The time horizon of this model is lifetime. The justification for this is that the impact of HCV accrues over a period of decades and, therefore, a lifetime is the appropriate time horizon to capture differential impact of treatment on health, utility and costs. This is also in line with other economic evaluations of HCV.

They cycle length of the model is that of 1 year. The justification of this is that this is consistent with previous economic models and reflects the relatively slow progression rate for chronic HCV.

A half cycle correction is applied which is consistent with previous economic models.

A discount of 3.5% was used (for both effects and costs) which is consistent with previous economic models and the NICE Guide to Methods of Technology Appraisal.

Beyond the treatment phase, the model defines patterns of disease progression over the remaining life of the patient, with the single treatment-related assumption that viral eradication early in the course of the disease prevents further</td><td>Q80K genotype will be excluded from treatment with simeprevir.</td><td colspan="7">
<table>
<tr><th></th><th>Cost</th><th></th><th>Outcome</th><th></th><th>ICER</th></tr>
<tr><td>Treatment experienced GT4</td><td>PR</td><td>£36,781</td><td>£8,811</td><td>10.732</td><td>0.990</td><td>£8,896</td></tr>
<tr><td></td><td>SMV/PR</td><td>£45,591</td><td>-</td><td>11.722</td><td>-</td><td></td></tr>
<tr><td>Treatment naïve F3-4 (GT1)</td><td>SMV/SOF</td><td>£69,170</td><td>-</td><td>11.747</td><td>-</td><td>-</td></tr>
<tr><td></td><td>No treatment</td><td>£32,465</td><td>£36,705</td><td>9.369</td><td>-2.379</td><td>£15,431</td></tr>
<tr><td></td><td>SMV/PR</td><td>£43,051</td><td>£26,119</td><td>11.341</td><td>-0.406</td><td>£64,305</td></tr>
<tr><td></td><td>TVR/PR</td><td>£48,786</td><td>£20,384</td><td>11.002</td><td>-0.745</td><td>£27,365</td></tr>
<tr><td></td><td>BOC/PR</td><td>£57,518</td><td>£11,652</td><td>10.478</td><td>-1.269</td><td>£9,182</td></tr>
<tr><td>Treatment experienced F3-4 (GT1)</td><td>SMV/SOF</td><td>£68,147</td><td>-</td><td>11.761</td><td>-</td><td>-</td></tr>
<tr><td></td><td>No treatment</td><td>£33,045</td><td>£35,102</td><td>9.239</td><td>2.522</td><td>£13,917</td></tr>
<tr><td></td><td>SMV/ PR</td><td>£52,906</td><td>£15,241</td><td>10.307</td><td>1.454</td><td>£10,480</td></tr>
<tr><td></td><td>TVR/PR</td><td>£60,075</td><td>£8,072</td><td>10.182</td><td>1.579</td><td>£5,113</td></tr>
<tr><td></td><td>BOC/PR</td><td>£67,673</td><td>£474</td><td>10.257</td><td>1.504</td><td>£315</td></tr>
</table>

Subgroup analyses for comparators vs PR are shown in the table below.
<table>
<tr><th>Population</th><th>Treatment</th><th>Cost</th><th>Incremental cost PR vs comparator</th><th>QALY</th><th>Incremental QALY PR vs comparator</th><th>ICER PR vs comparator</th></tr>
<tr><td>Treatment</td><td>PR</td><td>£32,408</td><td></td><td>10.531</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Author (Year) [Cost Year]	Summary of model: Analysis or Model Type; Analysis Time Frame; and Rationale for Design and Time Frame	Patient Population, including Average Age	Interventions & Comparators, and Sequences of Treatments in the Model, if Applicable		Cost		Outcome		ICER
	disease progression. Data for this model of disease progression were derived from untreated patient data and were modelled, as far as possible, on information related to Western European patients. Costs have been inflated to 2012 values (from 2003–4 prices) using the HCHS Index from PSSRU. The model, design and structure were initially validated at an advisory board held in March 2013. The models were quality checked by the model developer, and a second consultancy provided a further review and quality check to validate the structure and functionality of the model.		**Treatment experienced, prior relapsers GT1**						
				SMV/ PR	£38,934	£6,525	11.618	1.087	£6,004
				TVR/PR	£42,517	£10,109	11.563	1.032	£9,795
				BOC/PR	£44,717	£12,309	11.474	0.943	£13,053
			Treatment experienced, prior partial responders GT1	**PR**	£35,593		10.209		
				SMV/PR	£45,342	£9,750	11.050	0.842	£11,584
				TVR/PR	£47,486	£11,893	11.062	0.854	£13,928
				BOC/PR	£49,928	£14,335	10.946	0.738	£19,435
			Treatment experienced, prior null responders GT1	**PR**	£35,942		10.173		
				SMV/PR	£45,756	£9,814	10.974	0.801	£12,249
				TVR/PR	£46,307	£10,365	10.952	0.779	£13,301
				BOC/PR	£55,723	£19,781	10.850	0.677	£29,234
			Treatment experienced, prior relapsers GT4	**PR**	£33,585	-	11.070	-	-
				SMV/ PR	£37,446	£3,861	12.418	1.348	£2,865
			Treatment experienced, prior partial responders	**PR**	£37,371	-	10.669	-	-
				SMV/ PR	£47,062	£9,691	11.772	1.103	£8,790

<table>
<tr><th>Author (Year) [Cost Year]</th><th>Summary of model: Analysis or Model Type; Analysis Time Frame; and Rationale for Design and Time Frame</th><th>Patient Population, including Average Age</th><th>Interventions & Comparators, and Sequences of Treatments in the Model, if Applicable</th><th>Cost</th><th>Outcome</th><th>ICER</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>GT4</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Treatment experienced, prior null responders GT4</td><td>PR</td><td>£37,786</td><td>-</td><td>10.625</td><td>-</td><td>-</td></tr>
<tr><td>SMV/ PR</td><td>£48,202</td><td>£10,415</td><td>11.325</td><td>0.700</td><td>£14,889</td></tr>
</table>

Scenario analyses included: % eligible for response-guided treatment on boceprevir, change in gender split, different baseline characteristics, change in METAVIR split, change in PEG-IFN 2a vs 2b split, change in genotype 1a vs 1b split, different time horizon, change in transitions within natural history stage, excluding null responders, change in transition probabilities used, change in SVR rates, change in value of on-treatment decrement, change in value of SVR utility increment and time at which this is added and change in cost of liver transplant. These analyses were presented but not extracted. (Only the ones relevant to GT4 model were performed for GT4)

The ERG noted an error in the calculation of the cost of ribavirin in the genotype 1 model and the wrong health sates costs in the SMV/SOF model (inflated to 2011/12 costs rather than 2012/13). Correction data was presented but not extracted.

The ERG also conducted the following scenarios that were not extracted:
• Using ONS data for all-cause mortality in genotype 1 patients
• ITT analysis for simeprevir trials (i.e. including Q80K positive and negative patients)
• SVRs by separate baseline fibrosis grades for peginterferon alfa and ribavirin taken from the pooled QUEST 1 and 2 trials
• 1.5% discount rate for costs and outcomes
• Variations in the transition probability between SVR achieved in the F4 (compensated cirrhosis) health state and the HCC / DCC health states
• Variations in the transition probability between the F4 and DCC health states
• Changes in the treatment duration for telaprevir and boceprevir
• Alternative SVRs for genotype 4 patients
• An older baseline age for patients intolerant to or ineligible for interferon alfa treated with SMV+SOF</td></tr>
<tr><td>Westerhout 2015 [2013]</td><td>A state transition Markov model was used to create a cost-utility analysis.</td><td>Treatment-naïve and treatment-experienced patients chronically</td><td colspan="4">Treatment duration for SMV + PR is 24 weeks (12 weeks SMV + PR followed by 12 weeks PR alone) for treatment naïve patients and those with a prior relapse. Prior non-responders receive an additional 24 weeks of PR treatment.

In the PR, TVR + PR and BOC + PR regimens, all treatments are given 48 weeks to all patient types. Full details of</td></tr>
</table>

<table>
<tr><th>Author (Year) [Cost Year]</th><th>Summary of model: Analysis or Model Type; Analysis Time Frame; and Rationale for Design and Time Frame</th><th>Patient Population, including Average Age</th><th>Interventions & Comparators, and Sequences of Treatments in the Model, if Applicable</th><th>Cost</th><th>Outcome</th><th>ICER</th></tr>
<tr><td></td><td>The model shares an overall approach with previously published economic analyses in the field of hepatitis C treatment. It is composed of two phases. The first - 'treatment' phase - relates to the initial anti-viral treatment period. This phase includes up to 48 weeks of treatment followed by a 12-24 week post treatment period, at which point viral response is assessed. Based on the outcome, patients move into a second 'post treatment' Markov phase of the model after 72 weeks, which captures long term outcomes over the patients' remaining lifespan.

Health states of the model include: F0-F2 SVR, F3 SVR, F4 SVR, Mild HCV (F0-F2), Moderate HCV (F3), Compensated cirrhosis (F4). Decompensated cirrhosis, Hepatocellular carcinoma, Liver transplant, Post-liver transplant and death.

Cycle length in the Markov phase is 1 year, with a lifetime horizon. Half cycle correction is applied.

Both costs and benefits are discounted at 3.5% per year and are assessed from the</td><td>infected with genotype 1 HCV in the UK.

Treatment experienced patients were further split into prior relapsers, prior non-responders and prior partial responders.

Genotype 1a patients who exhibit the Q80K polymorphism are excluded from the model, following SMV + PR label recommendations.

Patients baseline characteristics:
• Age 50.0 years
• 71.2% male
• 79.0kg weight

Baseline disease severity (treatment naïve):
• 45.0% F0-F2
• 35.0% F3
• 20.0% F4</td><td colspan="4">treatment duration are given in supplementary table 1 of the publication.

<table>
<tr><th>Population</th><th>Drug regimen</th><th>QALYs</th><th>Incremental QALYs (SMV/PR vs comparator)</th><th>Costs</th><th>Incremental costs (SMV/PR vs comparator)</th><th>ICER (SMV/PR vs comparator)</th></tr>
<tr><td rowspan="4">Treatment naive</td><td>SMV/PR</td><td>12.776</td><td>-</td><td>£36,298</td><td>-</td><td>-</td></tr>
<tr><td>PR alone</td><td>11.651</td><td>1.125</td><td>£25,358</td><td>£10,940</td><td>£9,725</td></tr>
<tr><td>TVR/PR</td><td>12.618</td><td>0.158</td><td>£40,241</td><td>-£3,943</td><td>Dominant</td></tr>
<tr><td>BOC/PR</td><td>12.570</td><td>0.206</td><td>£41,099</td><td>-£4,801</td><td>Dominant</td></tr>
<tr><td rowspan="4">Treatment experienced</td><td>SMV/PR</td><td>11.359</td><td>-</td><td>£43,962</td><td>-</td><td>-</td></tr>
<tr><td>PR alone</td><td>9.843</td><td>1.515</td><td>£32,113</td><td>£11,849</td><td>£7,819</td></tr>
<tr><td>TVR/PR</td><td>11.282</td><td>0.077</td><td>£45,515</td><td>-£1,553</td><td>Dominant</td></tr>
<tr><td>BOC/PR</td><td>11.194</td><td>0.165</td><td>£51,258</td><td>-£7,296</td><td>Dominant</td></tr>
</table>

Scenario analyses - 1) age, gender and Metavir profiles and 2) health state transition probabilities were performed but not extracted. The publication also reports that treatment experienced patients were split into prior relapsers, prior non-responders and prior partial responders but the results of these subgroups are not reported.</td></tr>
</table>

Author (Year) [Cost Year]	Summary of model: Analysis or Model Type; Analysis Time Frame; and Rationale for Design and Time Frame	Patient Population, including Average Age	Interventions & Comparators, and Sequences of Treatments in the Model, if Applicable	Cost	Outcome	ICER
	perspective of the National Health Service in England. All costs were inflated to 2013 prices using the HCHS Pay and Prices Index. The approach adopted by this study is very similar to that used for previously published cost-effectiveness analyses of treatments for HCV, including models previously developed for comparators assessed in the current evaluation. The model fully complies with the 36 criteria listed in the critical appraisal tool recommended by NICE to assess the quality of economic analyses.	Baseline disease severity (treatment experienced): • 25.0% F0-F2 • 45.0% F3 • 30.0% F4 HCV subtypes: • 27.3% were genotype 1a • 72.7% were genotype 1b • 29.2% of genotype 1a had the Q80K mutation Prior treatment response (treatment experienced): • 40% were relapsed patients • 35% were partial responders • 25% were null responders				

Table 31: Additional Quality Assessments for Simeprevir Studies Identified in the Cost-effectiveness Review

	NICE TA331	Westerhout 2015
Study design		
1. Was the research question stated?	Y	Y
2. Was the economic importance of the research question stated?	Y	Y
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Y – NHS and Personal Social Services perspective	Y – perspective of the National Health Service in England.
4. Was a rationale reported for the choice of the alternative programs or interventions compared?	Y – considered current NICE guidance and current treatment practices.	Y – using current treatment practices although it does mention that "In the past 12 months, regimens using sofosbuvir with either SMV or ribavirin alone have been licensed" but that this was not modelled.
5. Were the alternatives being compared clearly described?	Y	Y
6. Was the form of economic evaluation stated?	Y – cost-effectiveness	Y – cost-utility
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Y	Y
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Y – sources given for all SVR values	N – an MTC was performed after an SLR but references for the studies found in the SLR are not given.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	NA

	NICE TA331	Westerhout 2015
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Y – MTC was used for the comparators SVR rates and all sources given with details of the study. For SMV/SOF trial data was used. Mixed treatment comparison and matching-adjusted indirect comparison were performed for the SVR values. A comprehensive search was performed for the comparators. Details of studies (eg double blinded) were given and patient characteristics. Meta-analyses based on direct comparisons were carried out between each pair of treatments when possible	Y - a mixed treatment comparison (MTC) was carried out, incorporating both direct and indirect evidence to derive relative SVR data for all treatments with odds ratios developed. SMV SVR was based on the Q80K negative population, reflecting its label recommendation. The efficacy of the BOC + PR RGT regimen was conservatively based on data from the fixed duration arm, showing a greater SVR rate
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y – QALYs	Y – QALYs
12. Were the methods used to value health states and other benefits stated?	Y – Hartwell data used, taken originally from Wright et al. and is EQ-5D TTO data.	Y – For disutilities, EQ-5D valuation index was used, day 1 EQ-5D scores were compared with the average scores captured during the period of treatment and applying UK preference tariffs to arrive at a utility estimate. Data for TVR and BOC were obtained from European HTA assessments. Utilities were derived from EQ-5D scores for patients in the UK Mild HCV trial as well as other sources

	NICE TA331	Westerhout 2015
13. Were the details of the subjects from whom valuations were obtained given?	NC – general description of patients was given (Hartwell and Wright) but not baseline characteristics. For SMV studies were found using EQ-5D and FFS and WPAI and population characteristics of all the studies were given (but these were only used in a scenario not the base case)	N – Sources were given but not a description of the trials or details of the population.
14. Were productivity changes (if included) reported separately?	NA – productivity was not mentioned	NA – productivity was not mentioned
15. Was the relevance of productivity changes to the study question discussed?	NA – productivity was not mentioned	NA – productivity was not mentioned
16. Were quantities of resources reported separately from their unit cost?	Y – drug costs reported separately from dosages, unit costs of resources given and Markov traces given in appendices so you could calculate how many patients were in each health state at a specific time.	Y – costs for health states were given but a Markov trace was not
17. Were the methods for the estimation of quantities and unit costs described?	Y – SLR performed to find costs or used most recent list prices	Y – drug costs were taken from list prices, treatment monitoring costs and AE management, health state costs were based on a previously published analysis. Where costs could not be sourced estimates were obtained through interviews.
18. Were currency and price data recorded?	Y – 2012 values, pounds	Y – pounds, 2013
19. Were details of price adjustments for inflation or currency conversion given?	Y – inflated to 2012 using the HCHS index from PPRSU	Y - All costs were inflated to 2013 prices using the HCHS Pay and

	NICE TA331	Westerhout 2015
		Prices index
20. Were details of any model used given?	Y	Y
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Y - based on previously published models.	Y – based on previously published model
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Y – lifetime	Y – lifetime
23. Was the discount rate stated?	Y – 3.5%	Y – 3.5%
24. Was the choice of rate justified?	Y – consistent with previous economic models.	Y – although the authors did not justify it, this is consistent with previous economic models.
25. Was an explanation given if cost or benefits were not discounted?	NA	NA
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Y – CI and distribution given for SVR rates, adverse events, utilities, transition probabilities	Y – CI given for SVR rates, transition probabilities, utilities, costs
27. Was the approach to sensitivity analysis described?	Y – Scenario analyses performed, DSA and PSA	Y – DSA and PSA performed and scenario analyses.
28. Was the choice of variables for sensitivity analysis justified?	Y – SVR transition probabilities, costs, utilities, adverse events,	Y – transition probabilities, health state utilities, and costs.
29. Were the ranges over which the parameters were varied stated?	Y – CI or 25%	Y – either CI or +/- 20% were used and distributions given.
30. Were relevant alternatives compared in the incremental analysis?	Y	Y
31. Was an incremental analysis reported?	Y	Y

	NICE TA331	Westerhout 2015
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Y	Y
33. Was the answer to the study question given?	Y – in the form of comparison of ICERs	Y – in the form of a discussion of the ICERs and PSA
34. Did conclusions follow from the data reported?	Y	Y
35. Were conclusions accompanied by the appropriate caveats?	Y – limitations of the model and the data used were given.	Y – strengths and limitations of the model were discussed.

Excel model

C2. The Excel model provided contains multiple hidden rows, hidden columns, hidden worksheets and cells with a white background containing white text (that is, these are not visible).

a. Please unhide all rows, columns, worksheets and make all text in cells visible (for example, changing the font colour from white to black for cells with a white background).

Response

The model contains some hidden rows, columns, worksheets and text to ensure the model is user-friendly and transparent. Anything hidden is irrelevant to the HCV genotype selected in the model, or the current model calculation. Default parameter values are hidden to avoid being accidentally overwritten. The model automatically unhides and rehides data when the model population is changed, and so it is not possible to provide a version of the model where the rows and columns are unhidden. Sheets and text can be manually unhidden by the user.

C3. Only two comparators can be considered simultaneously in the economic model, please provide a description of the methods used to construct CEACs including all comparators for each subgroup (including the technical implementation in the Excel file).

Response

The model contains the functionality to create a CEAC with multiple comparators. To do this, go to the 'PSA Multiple CEAC' tab in the model and click the 'Run PSA Multiple analysis' button. If the results include comparators that should be removed from the CEAC, then you can select the CEAC simulation output from the hidden 'PSA_MultCEAC_Output' sheet, paste to a separate sheet, remove any comparators that are not required and generate a CEAC using standard methods.

Model structure

C4. In Figure 16, page 192 of the company submission, there should be a connection between the compensated cirrhosis and hepatocellular carcinoma health states. Please confirm this and provide a corrected version of Figure 16.

Response

It was felt that Figure 16 was already very complex due to the number of states and possible transitions, and so the transition from compensated cirrhosis to hepatocellular carcinoma was not indicated, because an arrow cannot be clearly placed across the schematic. We can confirm that this transition is possible (as noted in Table 81: Transition probabilities used in the model).

C5. During the on-treatment period, patients are not allowed to die or to transit to more advanced disease stages (for example compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma).

a. Please include background mortality during the on-treatment period in the cost effectiveness analysis;

b. Please provide the results of all base case analyses for all subgroups presented in the company submission based on this amendment of the cost effectiveness model;

c. Please provide the results of all further analyses requested in this clarification letter based on this amendment of the cost effectiveness model.

Response

We acknowledge this point; however, inclusion of background mortality during the on-treatment period in the cost effectiveness analysis or providing transitions to more advanced disease stages while on treatment (for example, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma) would require significant structural changes to the economic model which is not feasible due to its complexity. Given that the model has to accommodate treatments with a range of different durations, it is not straightforward to implement these new transitions. However, the impact of the modelling assumptions on the cost-effectiveness results is expected to be very minor (a few weeks' worth of transitions in a lifetime time horizon model), and omitting these transitions favours those treatments with longer treatment durations. This simplifying assumption is consistent with previous NICE appraisals for SOF and LDV/SOF, and the ERG for LDV/SOF acknowledged that the size of bias was 'likely to be small'.

C6. During the on-treatment period and the period between the end of treatment and the SVR assessment, patients are not allowed to progress to more advanced disease stages.

a. Please justify why patients are not allowed to progress to more advanced disease stages during these periods.

b. Please show the impact of this model assumption on the results through a sensitivity analysis where patients are allowed to progress to more advanced disease stages during the on-treatment period and the period between the end of treatment and the SVR assessment.

Response

Please see the response to section C5. We acknowledge this point; however, providing transitions to advanced disease stages in the period between treatment end and SVR assessment would require fundamental structural changes to the economic model which is not feasible. The impact of the modelling assumptions on the cost-effectiveness results is expected to be very minor (a few weeks' worth of transitions in a lifetime time horizon

model), and omitting these transitions favours those treatments with longer treatment durations. This simplifying assumption is consistent with previous NICE appraisals for SOF and LDV/SOF, and the ERG for LDV/SOF acknowledged that the size of bias was 'likely to be small'.

C7. Several model structure assumptions have been made that are inconsistent with previous health economic models.

a. Please justify why no transition between hepatocellular carcinoma and liver transplant is incorporated in the base case.

Response

It is considered inappropriate and unreflective of clinical practice to model a transition from HCC to liver transplant, an assumption which has been validated by external expert clinical opinion (see SOF and LDV/SOF NICE appraisals, TA106, Shepherd, 2007 (5)) and as has been previously accepted as appropriate in TAs (TA330 and TA363). There is provision within the model to provide a parameter for this transition but no data were identified, and so for the basecase analysis it is assumed that people with hepatocellular carcinoma do not receive a liver transplant. This parameter is varied in the DSA (minimum 0, maximum 0.1, as an assumption).

The patient transition from hepatocellular carcinoma to liver transplant, rather than representing a change in clinical state, is actually one of a series of intervention options based upon individual clinical judgement and taking into account variables related tumour status (size and number of nodules, their vascular invasion, nodal involvement and metastatic spread) underlying liver function (Child-Pugh) and functional health status.

According to current European clinical guidelines, the allocation to therapy is guided by the use of the Barcelona-Clinic Liver Cancer classification which divides patients into 5 stages (0, A, B, C and D). The guidelines are presented in Figure 1.

Figure 1: European clinical guidelines on therapy for HCC

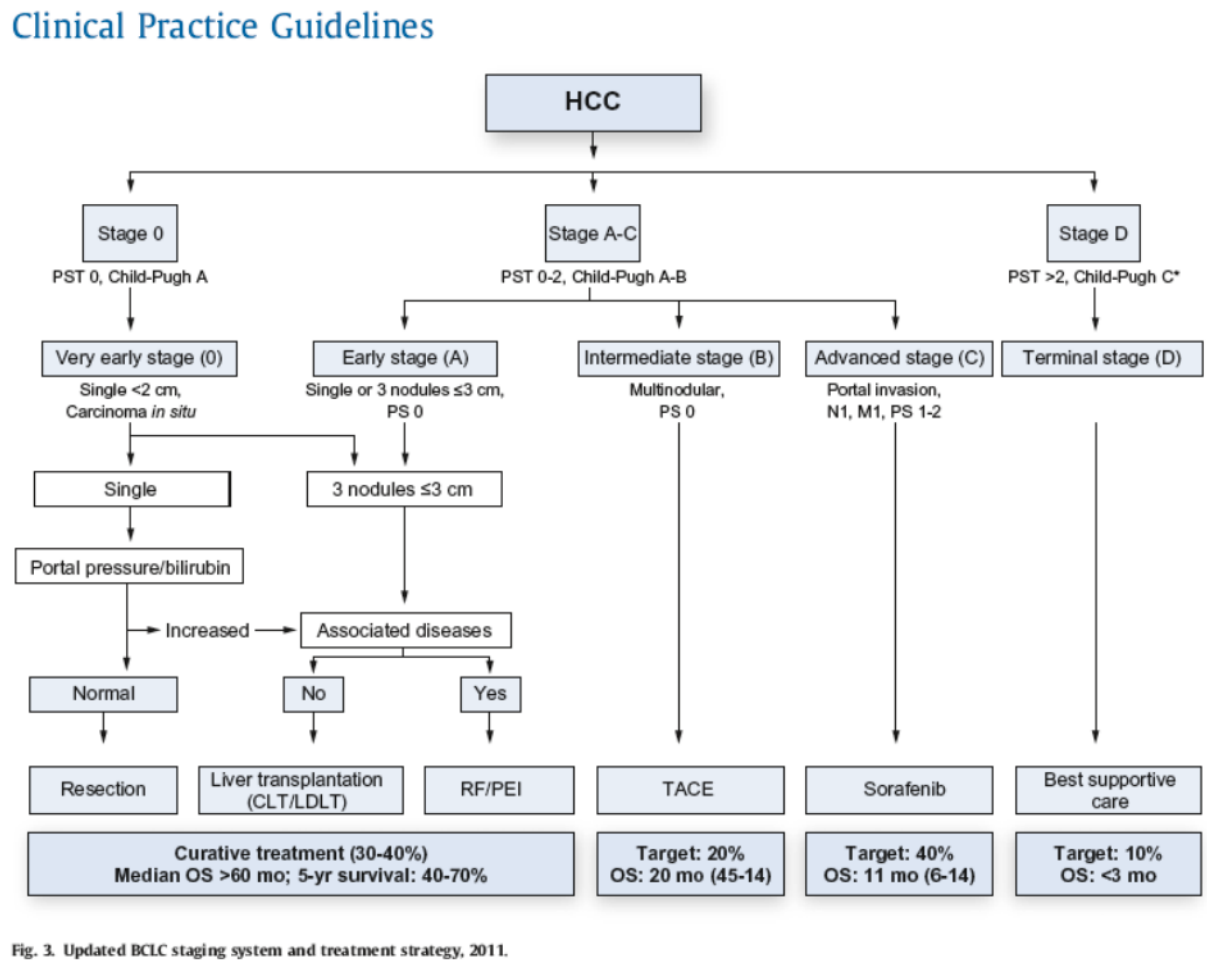

Fig. 3. Updated BCLC staging system and treatment strategy, 2011.

Liver transplantation is considered to be the first-line treatment option only for a subset of patients with early stage disease - single tumours less than 5cm or less than 3 nodules of less than 3cm in size, without associated disease (Milan criteria) - dependent on availability of a matched donor organ (6).

Local tumour ablation with radio-frequency (RF) or percutaneous ethanol injection is much more common as surgical management. As such, and as validated by external expert clinical opinion, it is deemed appropriate not to include a transition between hepatocellular carcinoma and liver transplant.

b. Please justify why no transition was incorporated for “SVR non-cirrhotic” to “non-cirrhotic” in the base case. Similarly for “SVR cirrhosis” to “cirrhosis” and “SVR decompensated cirrhosis” to “decompensated cirrhosis”.

Response

As discussed in Section 5.10.3 of the company submission, the economic model does not consider re-infection after a patient has achieved an SVR. This is a simplifying assumption that was validated by external clinical experts and an independent health economist. However, while we accept that the model may not appropriately consider the small number of patients with CHC who are re-infected after achieving SVR and may therefore somewhat over-estimate the cost-effectiveness of all active treatments within the model, the available clinical literature suggests that the re-infection rate in practice is very low.

In a systemic review and meta-analysis of studies which attempted to quantify HCV reinfection amongst active drug injectors (7) the pooled risk of reinfection (across 5 studies) was 2.4 per 100 person-years (95% CI, 0.9 – 6.1); in a stratified analysis of those who confirmed injection drug use post treatment, this was 6.4 per 100 person-years (95% CI, 2.49 – 16.69). The authors concluded that this constituted a low risk or reinfection, indeed lower relative to the incidence of new HCV infection in active injectors outside the setting of treatment (6.1 – 27.2 per 100 person-years) (8). While these estimates of re-infection rate are uncertain, they do provide evidence to demonstrate that spontaneous clearance of the same reinfection genotype is “fairly common” and is associated with biologically plausible underlying mechanisms, mediated through the induction of a variable degree of development of adaptive protective immunity post treatment.

In addition, it should be noted that the model also does not consider the reduction of onward HCV transmission to other infected persons at risk due to improved treatment success associated with SOF/VEL relative to current treatment options. The potential for reduction of HCV transmission with SOF/VEL is expected to be particularly high given the pan-genotypic efficacy of this treatment. The potential benefit of SOF/VEL in alleviating the public health burden of CHC in England is therefore likely to be underestimated and could be said to more than offset the reinfection effect noted above.

This modelling assumption was extensively discussed during the NICE Appraisal Committee meetings for the SOF and LDV/SOF appraisals, during which the Committee felt it was appropriate not to include this transition in the basecase economic model. For these reasons, the lack of incorporation of the risk of re-infection in the economic model is considered justifiable.

c. Please justify how the values used in the sensitivity analyses (presented in Table 219 of the company submission) regarding the above assumptions (see C7b; and described below Figure 16 of the company submission) are selected.

Response

In the basecase analysis of the model, reinfection is not considered (e.g. transition from SVR states to the equivalent non-SVR state). In the DSA, the transition probabilities for re-infection from ‘non-cirrhotic with SVR’ and ‘compensated cirrhosis with SVR’ are not varied, although that can be set to user-defined assumptions as a scenario analysis. The model DSA input settings currently vary the transition probability from ‘DCC with SVR’ to ‘DCC’ (re-infection) from 0.0 (minimum and basecase) to 0.1 (maximum) as an assumption. This is an error but does not impact on the basecase results or any of the DSA results presented in the company submission.

d. Please clarify what the expected impact of not distinguishing between no cirrhosis and mild cirrhosis (that is, combining METAVIR scores F0 – F3 in one health state) would be on the results.

Response

The model does not distinguish between no cirrhosis and mild cirrhosis (by METAVIR score), because the current structure offers the best fit for the SOF/VEL Phase III trials. Also, in clinical practice, liver biopsy, which is the only way to estimate the METAVIR score difference between these disease stages, is no longer standard practice in the UK CHC treatment pathway. This has been superseded by the use of non-invasive ultrasound elastography, such as Fibroscan™.

It is not possible to estimate what the results would be for a model that does distinguish between no cirrhosis and mild cirrhosis, and incorporating this would require a complete re-build of the economic model. There is some emerging evidence from another economic model which suggests that treatment of HCV irrespective of fibrosis stage is cost-effective compared to restricting treatment until F3 or F4 stage (9).

Comparators

C8. Page 198 of the company submission states “Some comparators of relevance to the decision problem were not included in the original economic model, and because of the way in which the economic model was constructed it was not possible to introduce these into the base-case analyses.” It is not clear what the company meant by this statement and which comparators are referred to.

a. Please clarify which comparators are being referred to and provide specific reasons why the construction of the economic model did not allow to incorporate these comparators in the base case;

Response

The economic model omits a small number of comparator treatments in some specific sub-populations (specifically, SOF+DCV+RBV 24w in GT3 cirrhotic patients, DCV+Peg-IFN+RBV 24/48w in GT4 patients, SIM+Peg-IFN+RBV (RGT) in GT4 patients and ombitasvir/paritaprevir/ritonavir 24w in GT4 cirhotic patients). Despite this, cost-effectiveness results have been obtained for all of these treatments by making very clear and pragmatic modelling assumptions. Analyses involving all of these treatments have been presented as scenario analyses in the company submission, including details of the modelling assumptions that have been made (Section 5.8.3). It should be noted that two of these treatments (DCV+Peg-IFN+RBV 24/48w in GT4 patients and SIM+Peg-IFN+RBV (RGT) in GT4 patients are irrelevant to clinical practice in the UK, reflected by their omission from relevant treatment guidelines, as described in Section 3.6 of the company submission. The other two treatments (SOF+DCV+RBV 24w in GT3 cirrhotic patients and ombitasvir/paritaprevir/ritonavir 24w in GT4 cirrhotic patients) are always dominated in the model economic analyses given the very high cost associated with 24w treatment regimens.

Therefore, the omission of these comparators from the original economic model is not expected to have any meaningful impact on the cost-effectiveness analysis, even though the omission has been appropriately dealt with via the scenario analyses outlined above.

Treatment effectiveness

C9. **Priority question** The company selected one study for each estimate of treatment duration in the economic model.

a. Please provide a random effect meta-analyses to obtain estimates of treatment duration for the economic model, for each comparator in each subgroup;

b. Please provide a new cost-effectiveness analysis based on the pooled estimates of SVR and safety as requested in B2a and the above requested pooled estimates of treatment duration

c. Please provide a full explanation why some studies were selected and others not for these meta-analyses.

d. Please also provide the requested analyses in C9a to C9c for comparators considered in scenario analyses only.

Response

For the vast majority of DAA-based treatments in the economic model, discontinuation rates are extremely low, as described in the company submission (Tables 91, 95, 99, 100, 106, 110, 114, 118, 122 and 126). Therefore, the treatment durations used in the model correspond very closely to recommended treatment durations in the Summaries of Product Characteristics for these treatments. It is therefore not considered informative to conduct a meta-analysis of treatment durations, given that alternative sources of data are not generally available for DAA-based treatments (see response to B.2). However, while the treatment durations for DAA-based regimens in the economic model correspond very closely to recommended treatment durations for these regimens, this is not the case for Peg-IFN+RBV treatment regimens. For example, in the GT3 TN NC subgroup in the economic model, the mean duration of the Peg-IFN+RBV 24w regimen is 21.0 weeks, reflecting the discontinuation rate on Peg-IFN+RBV 24w in the Phase III FISSION trial. To explore the impact on the cost-effectiveness results of this assumption, scenario analyses have been conducted in which the discontinuation rate has been set to 0% for Peg-IFN+RBV (24w for GT3 TN NC patients and 48w for GT1 TN NC patients). The results of these scenario analyses are presented in Table 32 and Table 33 and indicate that the ICERs for SOF/VEL 12w actually decrease relative to the basecase economic analysis, suggesting that the approach to treatment duration taken in the company submission is conservative and justified.

Table 32: Base-case results: GT3 treatment-naïve non-cirrhotic (discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Peg-IFN + RBV (24 wks)	[redacted]	20.85	[redacted]					
No treatment	[redacted]	18.12	[redacted]	£6,368	-2.73	-3.16	Dominated	Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	21.84	[redacted]	£18,958	0.99	1.25	£14,592	£14,592

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

Table 33: Base-case results: GT1 treatment-naïve non-cirrhotic (anticipated list price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	£16,304	18.97	13.63					
PegIFN + RBV (48 wks)	£23,187	20.37	15.22	£6,883	1.40	1.59	£4,329	Ext. Dominated
Ledipasvir/sofosbuvir (8 wks)	£29,713	21.73	17.10	£13,409	2.76	3.47	£3,868	£3,868
Simeprevir + PegIFN + RBV (RGT)	£33,817	21.40	16.61	£17,512	2.43	2.97	£5,890	Dominated
Sofosbuvir + PegIFN + RBV (12 wks)	£41,331	21.67	16.98	£25,027	2.69	3.35	£7,471	Dominated
Sofosbuvir/velpatasvir (12 wks)	£41,829	21.86	17.27	£25,525	2.89	3.63	£7,028	£73,604
Sofosbuvir + daclatasvir (12 wks)	£62,383	21.91	17.32	£46,079	2.94	3.69	£12,486	£349,606

ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN, pegylated interferon; QALYs, quality-adjusted life years; RBV, ribavirin.

Health related quality of life

C10. Please provide the rationale for the choice of the utility data from Wright et al (2006), apart from the fact that it was used in previous health technology appraisals.

Response

The utility data from Wright et al (2006) were used in the model because it was identified as the only high-quality UK source providing EQ-5D data in the systematic review of utility data (see Appendix 16).

C11. Please provide SF-36 utility data from the ASTRAL trials and use these data in a scenario analysis.

Response

SF-36 data from the ASTRAL trials has been presented in the company submission (Section 4.7). However, these data have not been formally mapped to produce SF-6D utility values for use in the economic model. However, by comparing the SF-36 data from the double-blind, placebo-controlled ASTRAL-1 trial (presented in Table 30 of the company submission) with the SF-36 data from the ION-1 trial of LDV/SOF (provided in Table 34), it is clear that the profiles are very similar.

Table 34: Summary of HRQL outcomes (ION-1)

Instrument	BL Mean (SD)	EOT Mean (SD)	PT Week 12 Mean (SD)	BL Mean (SD)	EOT Mean (SD)	PT Week 12 Mean (SD)	BL Mean (SD)	EOT Mean (SD)	PT Week 12 Mean (SD)	BL Mean (SD)	EOT Mean (SD)	PT Week 12 Mean (SD)
	LDV+SOF 12 weeks (N=162)			LDV/SOF+RBV 12 weeks (N=165)			LDV/SOF 24 weeks (n=165)			LDV/SOF+RBV 24 weeks (n=166)		
SF-36, Physical component	[redacted]											
SF-36, Mental component	[redacted]											
	LDV+SOF 12 weeks (N=214)			LDV/SOF+RBV 12 weeks (N=217)			LDV/SOF 24 weeks (n=217)			LDV/SOF+RBV 24 weeks (n=217)		
CLDQ-HCV	[redacted]											
FACIT-F Total score	[redacted]											
WPAI, percentage of overall work impairment	[redacted]											
WPAI, percentage of activity impairment	[redacted]											

Abbreviations: BL, baseline; 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; LDV, ledipasvir; PT, post-treatment; RBV, ribavirin; SD, standard deviation; SF-36, Short Form Health Survey; SOF, sofosbuvir; WPAI, Work Productivity and Activity Impairment.

[redacted]

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

Therefore, it is likely that the SF-6D utility values that would be mapped from the ASTRAL-1 trial would also be very similar to the SF-6D utility values obtained by mapping of the ION trial SF-36 data. In that sense it is considered justifiable to assume the same utility increment on-treatment with SOF/VEL as for LDV/SOF.

C12. During the on-treatment period, a treatment-specific utility increment/decrement is applied to the health state utility of patients:

a. Please justify why a multiplicative approach has been used to estimate on-treatment utility increment/decrement (and not an additive approach);

Response

The multiplicative method of applying a utility increment/decrement was applied to provide transparency in the relative change in utility when on treatment (expressed as a percentage). The multiplicative method for applying a utility increment/decrement is an accepted method for accommodating the impact of treatment (or a secondary condition) on patients' HRQL (10). This approach has been taken and accepted by NICE in the Gilead SOF and LDV/SOF appraisals (TA330 and TA363).

b. Please justify on which evidence these treatment-specific utility increments/decrements are based;

Response

The sources of all treatment-specific utility increments/decrements have been provided in the company submission (Tables 93, 97, 103, 104, 108, 112, 116, 120,124 and 128). These utility increments/decrements are generally consistent with previous Gilead SOF and LDV/SOF NICE appraisals (TA330 and TA363, respectively).

In general, treatment regimens including Peg-IFN or ribavirin are associated with tolerability profiles which reflect these agents. For example, events that are well characterised with the use of both Peg-IFN as well as RBV include mood and psychiatric disturbance, nervous system effects, diarrhoea and nausea, generalised systemic effects such as reduced appetite, asthenia, itch and inflammatory skin disorders and pain – including muscular and joint pain. Given this poor tolerability profile, the available clinical data, as outlined in the Tables listed above, support the HRQL/utility decrements associated with these treatments. Conversely, DAA treatments which omit the effects of Peg-IFN and RBV are observed to be associated with on treatment increments in HRQL/utility due to the rapid early suppression of replicating virus as an inflammatory stimulus and burden. These treatments are therefore associated with small utility increments while patients receive treatment. While this approach is justifiable in the context of the tolerability profiles of Peg-IFN, RBV and the DAAs, and the fact that it is consistent with previous NICE appraisals, the response to part c of this clarification question explores the (negligible) impact that the assumption of treatment-specific utility increments/decrements has on the overall cost-effectiveness results.

c. Please provide scenario analyses for all subgroups showing the impact of removing all treatment-specific utility increments/decrements.

Response

Due to time limitations, we cannot provide the full set of requested subgroups with all treatment-specific utility increments/decrements removed due to the significant amount of basecase results, and we expect that the impact will be negligible. Also, we do not believe it is informative to consider a full set of results without the impact of treatment-specific utility increments/decrements because these are clinical data showing the impact of a treatment on a patient's utility and these data must be incorporated to avoid misleading results.

However, for demonstration, we have provided the following comparative results in one patient subgroup, which shows that the impact of removing any on-treatment utility impact is negligible:

GT3 Treatment Naïve Non-cirrhotic

Table 35: GT3 Treatment naive non-cirrhotic - basecase results (SOF/VEL discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Peg-IFN + RBV (24 wks)	[redacted]	20.85	[redacted]					
No treatment	[redacted]	18.12	[redacted]	£6,368	-2.73	-3.16	Dominated	Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	21.84	[redacted]	£18,958	0.99	1.25	£15,199	£15,199

Table 36: GT3 Treatment naive non-cirrhotic - on-treatment utility increments/decrements removed - (SOF/VEL discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Peg-IFN + RBV (24 wks)	[redacted]	20.85	[redacted]					
No treatment	[redacted]	18.12	[redacted]	£6,368	-2.73	-3.22	Dominated	Dominated
Sofosbuvir/velpatasvir (12 wks)	[redacted]	21.84	[redacted]	£18,958	0.99	1.19	£15,956	£15,956

GT3 Treatment Naïve Cirrhotic

Table 37: GT3 Treatment naive cirrhotic - basecase results (SOF/VEL discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.36	[redacted]					
Peg-IFN + RBV (24 wks)	[redacted]	11.94	[redacted]	£1,408	2.59	1.61	£876	£876
Sofosbuvir/velpatasvir (12 wks)	[redacted]	16.89	[redacted]	£14,020	7.54	4.85	£2,892	£3,893
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	16.76	[redacted]	£23,937	7.40	4.73	£5,058	Dominated

Table 38: GT3 Treatment naive cirrhotic - on-treatment utility increments/decrements removed - (SOF/VEL discounted price)

Technology	Total			Incremental			ICER versus baseline	ICER incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment	[redacted]	9.36	[redacted]					
Peg-IFN + RBV (24 wks)	[redacted]	11.94	[redacted]	£1,408	2.59	1.64	£856	£856
Sofosbuvir/velpatasvir (12 wks)	[redacted]	16.89	[redacted]	£14,020	7.54	4.84	£2,896	£3,946
Sofosbuvir + Peg-IFN + RBV (12 wks)	[redacted]	16.76	[redacted]	£23,937	7.40	4.75	£5,037	Dominated

C13. Patients accomplishing sustained virological response are attributed a 0.04 utility increment.

a. Please justify on which evidence this increment is based (primary source) and why it applies in the current situation.

Response

This increment is based on data from the most recent source with the least uncertainty reporting SVR utility increments, Vera-Llonch et al 2013 (11). It should be noted that this utility increment has previously been used and accepted in both the SOF and LDV/SOF NICE Appraisals. In the SOF Appraisal (TA330), the Summary of the Appraisal Committee's key conclusions in respect of the utility increment on achieving SVR was as follows:

The Committee considered the use of different utility values in the economic model, from literature and the clinical trials. The Committee concluded that although alternative utility estimates from the pivotal studies would have been preferred, using the utility increment from Vera-Llonch et al. in its revised base case was acceptable.

Resource use and costs

C14. Health state costs for the non-cirrhotic health state are based on a weighted average of 83% F0-F2 (mild) and 17% F3 (moderate) HCV patients. These figures are *"derived from HCV TherapyWatch market research data."*

a. Please justify why this source was selected and clarify why it is considered to be relevant to the current decision problem;
b. Please provide this reference and/or an active web-link to the reference.

Response

HCV TherapyWatch Market Research Data

HCV TherapyWatch is a primary market research study conducted by Gilead Sciences in 5 EU markets. Data is not published and not available in public arena. Therefore, a reference or active web link is unavailable. However, the raw data from the market research and the relevant calculation is provided below.

A sample of physicians is asked to provide information regarding the patients under their care who have initiated treatment within the previous 12 weeks. The information provided in Table 39 below indicates the distribution of these patients according to Fibrosis score in 5 EU markets, including the UK.

Table 39: Fibrosis scores of patients treated in 5 EU markets

	F0 (%)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	Total (N)
France	3.1%	4.9%	19.4%	46.9%	25.7%	798
Germany	14.1%	28.7%	28.0%	20.7%	8.5%	661
Italy	2.0%	12.7%	19.1%	24.9%	41.2%	842
Spain	1.3%	2.4%	22.4%	34.3%	39.6%	835
UK	**12.0%**	**20.8%**	**19.5%**	**11.0%**	**36.7%**	**665**

Calculation for UK patients included in this market research

- For F0-F2 (mild disease): 12.0% + 20.8% + 19.5% =52.3%
- For F3 (moderate disease): 11%

Therefore, within the overall F0-F3 segment, F0-F2 accounts for approximately 83% and the F3 segment accounts for the remaining 17%.

These data are considered to be relevant to the Decision Problem because the health state utility data and health state cost data obtained from Wright et al and used in the economic model (see Response to C.10), provided utilities and costs for mild disease (F0-F2) and moderate disease (F3) separately. Therefore, the weighting calculated from the market research data was required in order to generate one health state utility value and one health state cost reflective of the 'non-cirrhotic' (i.e. F0-F3) disease state in the model.

C15. When NHS reference costs were used for resource use and costs (for example, Table 84 of the company submission)

a. Please provide the precise codes for the NHS reference costs and the precise method used to obtain the cost estimates (for example, taking a weighted average);
b. Please also provide the upper and lower quartile of the obtained estimates.

Response

The requested data is provided in Table 40.

Table 40: NHS reference costs and codes

Item	Unit cost	Cost year	Source	Details

Item	Unit cost	Cost year	Source	Details
OUTPATIENT APPOINTMENT				
Gastroenterology - Consultant Led Outpatient Attendances	£139.83	2014-2015	National Schedule of Reference Costs Year : 2014-15 (12)	All NHS trusts and NHS foundation trusts – Outpatient Attendances Data (service code 301)
Gastroenterology - Non Consultant Led Outpatient Attendances	£97.12	2014-2015	National Schedule of Reference Costs Year : 2014-15 (12)	All NHS trusts and NHS foundation trusts – Outpatient Attendances Data (service code 301)

An upper and lower quartile is not provided in the National Schedule of Reference Costs for these total outpatient attendance costs estimates.

C16. Please provide adverse event management costs (as described in Table 89 of the company submission) based on NHS reference costs and use these in scenario analyses for each comparator, in each subgroup.

Response

The NHS reference costs are not an appropriate source for the total adverse event management costs (as described in Table 89 of the company submission), which the model requires to ensure all costs associated with treatment are appropriately captured. To estimate the cost of diagnosing and treatment a range of adverse events (from mild to severe) we have used NHS Reference Costs (for outpatient and specialist attendances) and PSSRU unit costs (for GP attendances). We have used KOL opinion for resource usage and treatment protocols, and the BNF for medication costs. This approach is consistent with previous NICE appraisals for LDV/SOF and for SOF and all calculations and sources are reported in the company submission and model.

Model validation

C17. **Priority question** Please perform a cross-validation of the results, by providing, for each subgroup separately, a comparison of the total life years, quality-adjusted life years and costs for each comparator included in the current assessment with previous assessments: for example, TA330, TA331, TA365, TA363, TA 364 (both ERG and Company results), the studies identified in the cost effectiveness review from the company submission (Section 5.1) and studies mentioned in Clarification Question C1.

Response

We thank the ERG for their request and agree it is important to validate economic results to ensure they are appropriate for decision-making. However, we do not think it is appropriate to systematically cross-validate the economic results against previous NICE appraisals

because this is a separate appraisal focused on SOF/VEL within the remit of a Single Technology Appraisal.

Also, it should be emphasised that, where data are available, the model used for this SOF/VEL submission uses the most recent and appropriate data sources for many key parameters which will provide different economic results compared to older models and appraisals. Finally, many comparator therapies are subject to confidential PAS price discounts, and Gilead is not privy to their full company submissions and full results for previous NICE appraisals. For these reasons, and given the significant time constraints we do not believe it is feasible or useful to systematically compare the result of the SOF/VEL economic analysis against therapies from other manufacturers considered in previous NICE appraisals in a cross-validation exercise.

We believe the best and most informative analyses are those which provide a 'spot-check' cross-validation of the SOF/VEL and LDV/SOF cost-effectiveness results, given the consistency of the modelling approaches used and the very limited time available.. We have therefore presented the costs and QALYs of Harvoni (LDV/SOF) from the ERG's preferred analysis, between the SOF/VEL analysis, and the LDV/SOF appraisal (TA363). This was only possible in GT1 because GT4 was not modelled separately in TA363. Life Years Gained (LYG) were not reported by the ERG, and no results with a 12 week LDV/SOF regimen were presented for GT1 treatment experienced compensated cirrhosis. As shown in Table 41, where comparison was possible, both costs and QALYs were very similar for LDV/SOF (12 weeks).

Table 41: LDV/SOF results - current SOF/VEL model basecase

Population	Technology	Current basecase SOF/VEL model		LDV/SOF ERG report (Table 53)*	
		Costs	QALYs	Costs	QALYs
GT1 TN NC	Ledipasvir/sofosbuvir (8 wks)	£29,713	17.10	£29,523	17.12
GT1 TN CC	Ledipasvir/sofosbuvir (12 wks)	£60,349	9.88	£62,440	9.94
Population	**Technology**	**Current basecase SOF/VEL model**		**LDV/SOF ERG report (Table 54)[%]**	
		Costs	**QALYs**	**Costs**	**QALYs**
GT1 TE NC	Ledipasvir/sofosbuvir (12 wks)	£41,891	16.17	£42,032	16.12

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

[%] Central estimates of cost-effectiveness (additional analysis 3, use of alternative transition probabilities based on the sofosbuvir STA model)

C18. Please clarify how results of the model were externally validated (as described in Section 5.9 of the company submission).

Response

As detailed in Section 5.9.1, the draft report (section 5) was reviewed by an independent health economist who commented on the assumptions, results and interpretation of the results. It should also be noted that the modelling approach taken in the SOF/VEL appraisal closely follows that taken in the previous SOF and LDV/SOF NICE appraisals. Those economic models were also externally validated and used as the basis of the Technology Appraisal Guidance issued by NICE (TA330 and TA363, respectively).

References:

C10, Wright et al (2006): Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess. 2006 Jul;10(21):1-113, iii.

C11, ASTRAL Trials:

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11. Vera-Llonch M, Martin M, Aggarwal J, Donepudi M, Bayliss M, Goss T, et al. Health-related quality of life in genotype 1 treatment-naive chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. Aliment Pharmacol Ther. 2013 Jul;38(2):124-33.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Sofosbuvir- velpatasvir for treating chronic hepatitis C [ID921]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

About you and your organisation

Your name: [redacted]

Name of your organisation: The Hepatitis C Trust

Your position in the organisation: [redacted]

Brief description of the organisation: 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 4,500 members of our patient association.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

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 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. 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 2016/17 in apparent direct contravention of NICE technology guidance.

Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

A cure. For people with significant symptoms (and many more people than is commonly thought do experience symptoms – but they don't realise it until after a cure and disappearance of those symptoms) it can mean a whole new life

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Through our helpline, our support groups and other support services we are in touch with patients daily. Their experience of current NHS care is hugely variable. Many are receiving highly effective interferon-free therapy, are being cured and are generally delighted with the service and with being hepatitis C-free. However, many are also exasperated with the new Operational Delivery Networks (ODNs) through which all secondary hepatitis C care has been delivered since August 2015. These took some months to start functioning properly and there was great confusion about patients' eligibility for treatment and the timing of that treatment. This still persists because NHS England has

introduced ‘run rates’ which strictly limit how many patients can be treated each month by each ODN, irrespective of capacity. The new treatments with their very high efficacy, minor side-effects and short duration are extremely acceptable. They are much preferred to those regimens that still contain interferon. In particular, people with genotype 3 and mild disease do not have access to the most effective interferon-free therapy and are waiting impatiently for such a regimen.

What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

A cure (SVR) with consequent improvement in life expectancy and quality of physical, emotional, social, employment and sexual life

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

There are currently many treatments or combinations available. The main advantage is over those containing interferon, which is generally toxic and can have long-term complications.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None known

What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Lack of access for some

Waiting times because of NHSE's rationing

Continued use of interferon for some genotypes

Please list any concerns patients or carers have about the treatment being appraised.

None known

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None known

Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

People with genotype 3, 5 or 6 who do not generally have access to interferon-free therapy

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

None known

Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☑ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Not yet in clinical use

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, SVR which equates to a cure. Not aware of any limitations

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not currently available

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☑ Yes ☐ No

If yes, please provide references to the relevant studies.

Max Hopwood 'Recovery from hepatitis C treatments' University of New South Wales 2009

http://www.hepctrust.org.uk/Resources/HepC%20New/Hep%20C%20Resources/Reports/Recovery_from_hepatitis_C_treatments.pdf

The Hepatitis C Trust 'Post-treatment survey report' 2010

http://www.hepctrust.org.uk/Resources/HepC%20New/Hep%20C%20Resources/Reports/Post%20Treatment%20Survey%20Report%202010.pdf

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

N/A

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

N/A

Other issues

Do you consider the treatment to be innovative?

☑ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

It offers very effective interferon-free therapy for genotype 3 (45% of those with HCV in England) potentially at a price that makes it cost-effective (Sofosbuvir and Daclatasvir was found not to be cost-effective for those with mild disease). It is pan-genotypic, in trials achieving 95% SVR rates across all genotypes. This could potentially be the answer for people who are infected

with more than one genotype (where one genotype is eradicated through treatment leaving another to emerge) and mean that mistakes in genotyping (they do happen from time to time) will not matter. It will also potentially simplify treatment protocols. This could be important as we move towards a more public health approach to treatment, targeting groups that may not engage easily with services but where there is significant transmission. For example, in TB, the Find and Treat programme essentially puts people on treatment immediately following diagnosis and a similar approach is about to be trialled for hepatitis C. Simplification will help less specialised healthcare workers to deliver treatment (e.g. nurses, GPs, maybe even drug workers and pharmacists) allowing more treatment closer to patients as intended by the ODN set-up

Are there any other issues that you would like the Appraisal Committee to consider?

As usual, we would like the Committee to consider the cost averted by curing people who might otherwise continue to transmit infection.

Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This treatment could stop the use of interferon for all genotypes (interferon use risks long-term harm to patients)
- It could simplify the treatment protocol
- It could help ODNs increase treatment in the community, using e.g. nurses, GPs, even drug workers or pharmacists.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation:
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? ✓
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: Nil

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

What is the expected place of the technology in current practice?

The hepatitis C virus (HCV) is an infectious disease and an important cause of liver disease. Around 75% of people infected with hepatitis C will develop chronic infection. Chronic infection with hepatitis C, if left untreated or if unsuccessfully treated, can cause cirrhosis and liver cancer in a significant proportion of patients. Once cirrhosis has developed, hepatic decompensation and other potentially fatal complications can occur and liver transplantation may be required. Over 160,000 individuals are infected with HCV. There are 6 different genotypes of hepatitis C. The most common genotypes in the UK (~90%) are genotype 1 (G1) and genotype 3 (G3). Other genotypes include genotypes 2, 4, 5, and 6. HCV disease is asymptomatic in its early stages. The primary aim of treatment of HCV disease is to cure the infection by eradication of HCV, by achieving a sustained virological response (SVR) at week 12 post therapy.

Currently NHS England (NSHE) has guidance regarding [1] the treatment of HCV which will vary dependant on genotype and fibrosis stage of disease. This is based on a number of NICE guidances and also the treatment that at the time prescription the treatment that offers best "value for money, independent of NICE guidance. A variety of direct acting antiviral (DAA) therapies taken orally for 8–12 weeks alone or in combination with pegylated interferon and or ribavirin are recommended. First generation protease inhibitors such as boceprevir or telaprevir (in combination with pegylated interferon & ribavirin) are no longer used as these are less efficacious and have a higher side effect profile

Treatment options for individual cases are discussed at regional Operational Delivery Networks (ODNs) around the country. Treatment is limited in each ODN to a run rate dictated by NHSE (as low as 15 cases a month). Priority is given to those HCV patients with advanced hepatic fibrosis, cirrhosis or decompensated cirrhosis. NICE guidance is available for a number of different therapies for HCV (see appendix). Current treatment regimens have a greater than 90% cure rate for HCV with the exception of Hepatitis C genotype 3 with cirrhosis which in general has a sustained viral response rate of about 70-80%.

There is broad consensus of treatment regimens with international guidance from EASL [2] (European association for the study of the liver) and AASLD [3] (American association for the study of liver disease). These guidelines are well validated.

Regional differences within England do exist determined by NHSE "run rate". The infrastructure for treatment of HCV (diagnostic services and staffing) is well established nationally. Treatment with the new oral regimes can be with primary or secondary care in view of the low side effect profile with the exception of patients with decompensated cirrhosis who should be treated within secondary care.

Sofosbuvir-velpatasvir for treating chronic hepatitis C in particular may benefit those patients with HCV genotype 3 infection and cirrhosis, whose treatment with current regimes (pegylated interferon, ribavirin and sofosbuvir or sofosbuvir and daclatasvir) is sub-optimal with sustained viral response rates of 70-80%.

The advantages and disadvantages of the technology

Sofosbuvir-velpatasvir is an oral fixed dose combination of two antiviral pangenotypic anti HCV drugs. The major advantages of this technology are a low side effect profile, oral administration, one daily dosing and short duration of treatment of 12 weeks and thus better patient acceptability with extremely good efficacy for all HCV genotypes irrespective of stage of disease. Few interactions with other medications is an additional advantage. No additional investigations are required compared to current treatment regimes.

Indications for therapy are the same as other regimes with discontinuation of therapy only if untoward side effects are encountered by the patient with a fixed duration of treatment. In general less clinical monitoring of patients is required if the patient has well compensated liver disease and can avoid interferon therapy.

The major evidence base is from three multicentre trials published in late 2015 [4-6] which are applicable to UK practice. Two studies [4, 5] demonstrated in HCV genotypes 1a, 1b, 2, 3, 4, 5 and 6, after 12 weeks of treatment, a SVR 12 weeks post therapy of 97-100% indicative of virological cure. In HCV genotype 3, a genotype that is difficult to treat [5], a sustained viral response after 12 weeks of treatment was seen in 95% of non-cirrhotic patients and 89-91% in those who previously failed treatment or who had cirrhosis. Patients with HCV genotype 3 and decompensated cirrhosis have a poorer response to therapy. Nonetheless in the ASTRAL 4 study [6], the sustained viral response rates to 12 weeks treatment was 83%, increasing to 94% with the addition of ribavirin. In these patients an improvement in liver function was observed in almost 50% with serious adverse events in 16-19%. These results are very favourable compared to existing treatments for HCV G3 cirrhosis with decompensation. In all three studies the combination of sofosbuvir and velpatasvir was superior to study comparators with respect to completion of treatment, fewer serious side effects, and sustained viral response rates. The presence NS5a resistant associated variants did not affect outcomes in these studies, but it is likely that further studies will be needed particularly in the treatment of HCV G3.

Further data will be needed before treatment with sofosbuvir-velpatasvir of special HCV treatment groups such as HIV co-infected patients can be considered. Sofosbuvir therapy is contra-indicated in patients with advanced kidney disease.

Thus the most important outcome measures of treatment effectiveness, tolerability with improvement in liver function for those with decompensated disease were excellent and better than existing treatments. The surrogate marker of sustained viral response has been demonstrated from previous data to indicate long term survival benefit [7]. Thus far no adverse effects that were not apparent in clinical trials have come to light subsequently during routine clinical practice.

Any additional sources of evidence

No

Implementation issues

HCV ODN's are now established in England, having commenced in August 2015. These ODNs consist of HCV treatment groups of doctors, nurses, virological services with support from pharmacy and addiction services. These HCV treatment groups, usually based in large district general hospitals are well established but currently underutilised with the existing "run rates" dictated by NHSE. However,

if there is no limitation to the prescription of this technology, then further investment would be needed in staffing and diagnostic services as this technology is more effective and better tolerated than previous therapies, thus demand for HCV treatment would as increase compared to existing rates of service provision.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

No impact of equity of care will arise from this technology

1. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/06/hep-c-cirrhosis-polcy-statmnt-0615.pdf
2. http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf
3. http://onlinelibrary.wiley.com/doi/10.1002/hep.27950/pdf
4. Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, Abergel A, Mangia A, Lai CL, Chan HL, Mazzotta F. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. New England Journal of Medicine. 2015 Dec 31;373(27):2599-607.
5. Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, Lawitz E, Thompson A, Shiffman ML, Cooper C, Towner WJ. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. New England Journal of Medicine. 2015 Dec 31;373(27):2608-17.
6. Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, Reddy KR, Lawitz E, Flamm SL, Schiano T, Teperman L. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. New England Journal of Medicine. 2015 Dec 31;373(27):2618-28.
7. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. 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. Clinical Infectious Diseases. 2015 May 17:civ396.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: BASL / BVHG

Are you (tick all that apply):

- **a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes**
- **a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? No
- other? (please specify) No

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: *Nil*

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

What is the expected place of the technology in current practice?

This technology will be a very welcome addition to the therapies that have become and are becoming available for hepatitis C (HCV). It has shown very good efficacy (as measured by the recognised SVR endpoints) in all genotypes, with no significant toxicities or tolerability issues. The lack of requirement for Ribavirin as a co-medication will have benefits in some patients, and the high efficacy in genotype 3 is a very welcome benefit of this technology over the comparators. This is further supported by the fact that those with genotype 3 have, on average, a worse prognosis and faster disease progression untreated, and there is therefore a clinical unmet need at present.

There are very significant advantages in terms of tolerability and acceptability (as well as efficacy) compared to regimens containing interferon (which are still utilised in those with genotype 2 and 3).

The planned scope is comprehensive, but we would like to point out that the comparators Boceprevir, Telaprevir and Simeprevir are no longer utilised clinically within the UK. We appreciate however that comparisons with these technologies may still be required. Though it may not be permissible we would welcome a comparison with Elbasvir/Grazoprevir which is expecting EU licensing in the near future and is progressing through NICE appraisals.

The technology will be utilised in and provided from secondary and tertiary care settings, and out-reach settings supervised by these professionals (eg prison in-reach, drug services and other community locations).

The advantages and disadvantages of the technology

The comparator all-oral DAA regimens are of similar tolerability and are all easy to utilise. There are therefore no specific issues related to its use and implementation, or other practical implications to consider with this technology. The lack of ribavirin co-medication will be an advantage in terms of tolerability and pill burden, and the lack of interferon is a very significant advantage both for patients and for the clinicians monitoring treatment.

There are no specific stopping or early termination rules, and the length of the regimen is pre-decided based on factors such as cirrhosis and previous treatment experience, not on on-treatment response.

The evidence-base from the clinical studies would be expected to translate to real-life experience. This has been the case for similar regimens.

The patient groups studied encompass those patients with HCV within the UK.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

Any additional sources of evidence

All the data related to this technology are on-file with the manufacturer and derived from their trial programme, with the main data from their licensing studies. There are no studies, trials or other sources of data that require to be considered.

We especially welcome the planned review of impacts upon onward transmission of HCV, and on costs from the personal social services perspective.

If the data permits we would suggest that consideration is taken to assess this technology in those with F3 fibrosis (as this has developed into a separate category in HCV treatments); consider those with Child-Pugh B and C decompensated cirrhosis rather than the listed 'pre-transplant' group; and include any emerging data that becomes available on the use of this technology in those who have previously failed direct-acting antiviral treatment for HCV (especially NS5a exposed patients).

Implementation issues

There should be no implementation issues – the technology is easy to provide and monitor (particularly when compared to interferon-based therapy), and the physical and staffing infrastructures are already in place. No specific training would be required.

Equality

Different HCV genotypes differentially affect specific racial and other populations – for example genotype 3 in those from the Indian sub-continent, genotype 4 in those from Egypt. Some individuals are also from discriminated populations – such as those that inject drugs.
Therefore there may be a possibility of inadvertent discrimination, particularly in those groups with sub-optimal current therapies (eg genotype 3)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Stephen David Ryder

Name of your organisation
Nottingham University Hospitals NHS Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? no
- other? (please specify)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Hepatitis C currently has a complex treatment pathway in the NHS. The current recommendations and funding by NHS England limit treatment numbers and currently access to therapy is restricted predominantly to those with more advanced fibrotic liver disease although there is variation in caseload throughout the hepatitis operational delivery networks put in place by NHS England. The current treatment also varies by hepatitis C genotype, patients with genotype 1 (or 4) have access to either oral therapy with the Abbvie 3D regimen or Harvoni if they meet treatment thresholds or are put on "watchful waiting". The majority of patients currently follow the latter which is entirely driven by cost of medicines. Patients with genotype 2 or 3 still have initial therapy with interferon and ribavirin unless they have failed this therapy previously or have significant hepatic fibrosis when they can access sofosbuvir based oral regimens (genotype 2) or sofosbuvir with per interferon and ribavirin for genotype 3. Oral therapy for genotype 3 with sofosbuvir and daclatasvir is restricted to those with decompensated cirrhosis or those with a contraindication to interferon.

These regimens are outlined in clinical guidelines produced at a consensus meeting hosted by NHS England and supported by the professional organisations and commissioning policy produced by NHS England.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The main advantage of this technology compared to current therapy is the enhanced activity seen in genotype 3 infection. For genotypes 1,4,5 and 6 the technology is effective but results in terms of cure rates (SVR) and side effects are comparable to existing therapies (Harvoni and Abbvie 3D) and has the minor disadvantage of 12 v 8 weeks therapy for some patients versus Harvoni. The previous oral options for genotype 3 were limited by either poor effectiveness or high cost leading to the ongoing use of interferon based therapy with its poor side effect profile as current first line therapy. The major advantage of the technology is that it provides an oral treatment option for G2 patients with comparable SVR rates to G1 patients (95% or greater) and therefore represents the first drug combination which can be said to be truly pangenotypic.

There are no stopping rules and the treatment has a very good side effect profile.

I have experience of the technology in clinical trials and those trials do reflect current clinical practice in the UK, indeed the UK contributed significant numbers of patients to the key studies. We have seen very consistent translation of trial results in hepatitis C into therapy and I see no reason to feel that this technology will be less effective in clinical practice than it was in the trial environment.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I do not consider that the appraisal could exclude people protected by equality legislation. People with hepatitis C are often socially disadvantaged and from minority ethnic backgrounds but the technology would potentially improve access to treatment in those groups given its better side effect profile as compared to interferon.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The evidence will be found by the technology focussed review and the company submissions and I do not think any other data is available.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There is already significant restriction of existing NICE approved therapy due to budgetary constraints alone. The hepatitis ODNs have capacity to deliver treatment far in excess of current treated numbers now and this technology will enhance that given the level of clinical supervision required for all oral therapy is much lower than for interferon based treatments. There is therefore no restriction on clinical capacity to deliver this treatment.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: MR KELVIN MARSHALL
Name of your nominating organisation: LIVER4LIFE
Do you know if your nominating organisation has submitted a statement?

☐ Yes ☐X No

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐X No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐X Yes ☐ No

- a carer of a patient with the condition?

☐ Yes X☐ No

- a patient organisation employee or volunteer?

☐X Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☐X No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I CONTRACTED HEPATITIS C IN THE MID [redacted] WHILE TRAVELLING THROUGH CENTRAL ASIA, EITHER FROM DONATING BLOOD TO HOSPITALS IN THE REGION, OR HAVING DENTAL WORK CARRIED OUT IN INDIA. 35 YEARS LATER IN [redacted] I COLLAPSED WHILE TRAVELLING IN SOUTHEAST ASIA AND WAS RUSHED TO HOSPITAL WHERE I WAS DIAGNOSED WITH HEPATITIS C AND 8 OTHER SERIOUS HEALTH COMPLICATIONS RESULTING FROM IT, INCLUDING CHRONIC LIVER DISEASE AND DECOMPENSATED LIVER CIRRHOSIS. I HAD NEVER HEARD OF HEPATITIS C AND CERTAINLY DIDN'T KNOW ANYTHING WAS WRONG WITH ME UNTIL VERY SHORTLY BEFORE I COLLAPSED.

I RETURNED TO THE UK IN [redacted] [redacted] AND SUBSEQUENTLY WENT THROUGH 2 FAILED TREATMENT ATTEMPTS TO CLEAR THE VIRUS ([redacted] AND [redacted]) BEFORE BEING DIAGNOSED WITH LIVER CANCER IN [redacted] [redacted] RESULTING IN 2 LIVER TRANSPLANTS IN DECEMBER THAT YEAR. I FINALLY CLEARED THE VIRUS WITH GILEAD'S SOFUSBUVIR/LEDISPASVIR ON THE SOLUS 11 TRIAL IN [redacted]. I NOW RUN THE LIVER4LIFE HELPLINE AND SUPPORT MANY INITIATIVES TO IMPROVE AWARENESS OF HEPATITIS C.

(PLEASE SEE ATTENDUM ATTACHED FOR AN EXPANDED VERSION).

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

1. CURE, FAILING THAT
2. REDUCTION OF SYMPTOMS DURING TREATMENT, FAILING THAT
3. POSITIVE NEWS ON FORTHCOMING TREATMENTS THAT MIGHT CURE ME

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I WAS A NON RESPONDER AFTER 9 WEEKS OF DOUBLE THERAPY WITH INTERFERON/RIBAVIRIN, THE TOXICITY OF THIS DRUG COMBINATION MADE BE FEEL VERY MUCH WORSE THAN THE ALREADY DIFFICULT TIME I WAS HAVING WITH HEPATITIS C.

I LASTED 21 DAYS ON TRIPLE THERAPY WITH TELAPREVIR ADDED, I DON'T KNOW HOW I MANAGED EVEN THAT LONG ON THIS TREATMENT, BY THE 21ST DAY I HAD TO BE RUSHED INTO HOSPITAL WITH DERANGED ELECTROLYTES AND TO BE STABILISED. I WAS TAKEN OFF THE TREATMENT IMMEDIATELY.

BOTH DOUBLE AND TRIPLE THERAPY OCCURRED BEFORE MY 2 LIVER TRANSPLANTS. THE NEW DAA SOFUSBUVIR/LEDIPASVIR COURSE WAS TAKEN 17 MONTHS AFTER TRANSPLANT, I HARDLY NOTICED ANY SIDE EFFECTS FROM THIS TREATMENT AND THE VIRUS WAS UNDETECTABLE AFTER 28 DAYS, AND HAS REMAINED SO TO TODAY.

THE REACTION OF PATIENTS TO THESE DIFFERENT TREATMENTS I HAVE FOUND TO BE UNIFORM AMONG THOSE WE SEE COMING THROUGH OUR SWINDON HEP C POSITIVE SUPPORT GROUP.

SO WHY WOULD ANY PATIENT VOLUNTEER FOR OFTEN TOXIC OLD THERAPIES WHEN THE NEW DAA'S ARE SO EASY TO WITHSTAND IN COMPARISON?

THERE'S THE DILEMMA FOR NICE, THE COST IMPLICATIONS, BUT FROM A PATIENTS PERSPECTIVE, THERE CAN ONLY REALLY BE ONE CHOICE.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:
• the course and/or outcome of the condition

- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

WITH THE ASSUMPTION THAT SOFUSBUVIR/VELPATASVIR WORKS SIMILARLY TO SOFUSBUVIR/LEDISPASVIR, THE BENEFIT IS PATIENT CURE WITHOUT SOME SERIOUSLY NASTY SIDE EFFECTS THAT CAN THEMSELVES PRODUCE LONG LASTING DAMAGE. I FEEL MY MEMORY FURTHER DETERIORATED ON DOUBLE/TRIPLE THERAPY TREATMENT, AND HAS IN NO WAY RECOVERED FULLY SINCE.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

I HAVEN'T EXPERIENCED THIS PARTICULAR DRUG COMBINATION, SO AGAIN ASSUMING THE EFFICACY OF THIS DRUG IS SIMILAR TO OR BETTER THAN SOFUSBUVIR/LEDISPASVIR, AND IGNORING COST TO THE NHS, THE PATIENT EXPERIENCE THROUGHOUT TREATMENT WILL BE IMMEASURABLY BETTER, WITH HOPEFULLY LESS LONGER LASTING DAMAGE.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I CAN HONESTLY SAY MY VIEW WOULD BE SUPPORTED BY OVER 100 PATIENTS WHO HAVE ATTENDED OUR SUPPORT GROUP OVER THE LAST 18 MONTHS, MANY ON THE OLD TREATMENT, SOME ON THE NEW, AND PEOPLE LIKE MYSELF WHO HAVE EXPERIENCED BOTH THE OLD TREATMENTS AND THE NEW DIRECT ACTING ANTI-VIRALS.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

1. THE SIDE EFFECTS OF RIBAVIRIN. HEP C PATIENTS IN OUR SUPPORT GROUP CALL IT RIBORAGE, BECAUSE TAKING IT MAKES YOU FEEL ANGRY, THAT'S FINE IF YOU'RE NOT AN EX SUBSTANCE ABUSER AND LIVE A NORMAL LIFE, THESE PATIENTS CAN COPE REASONABLY WELL, BUT I HAVE COME INTO CONTACT WITH MANY EX SUBSTANCE ABUSERS WHO TEND TO HAVE MENTAL OR ANGER ISSUES TO DEAL WITH ANYWAY (HENCE SUBSTANCE ABUSE), THIS TREATMENT IS SO MUCH MORE DIFFICULT FOR THEM.

2. THE SIDE EFFECTS OF INTERFERON. MOST PATIENTS I TALK TO SUFFER VARYING DEGREES OF 'UNWELLNESS' AFTER INJECTION THAT CAN LAST SEVERAL DAYS, AND CAN BE EXTREME. PUTTING PATIENTS THROUGH A REPEATING CYCLE OF INTERFERON SIDE EFFECTS TO COPE WITH IN ADDITION TO THE SYMPTOMS OF HEP C. YOU HAVE TO BE VERY FOCUSSED

AND DEDICATED TO CURE TO GO THROUGH INTERFERON TREATMENT.

3. THE SIDE EFFECTS OF TELAPREVIR. HOW DO YOU EAT 20 GMS OF FAT EVERY TIME YOU TAKE THIS DRUG WHEN YOU'RE ALREADY NAUSEOUS, TIRED, WITH A HEADACHE, BRAIN FOG, AND HAVE ZERO APPETITE? IT'S A TRULY AWFUL EXPERIENCE THAT AGAIN REQUIRES MUCH SUFFERING AND PATIENT DEDICATION TO WITHSTAND.

4. LONG TERM MEMORY LOSS AS DESCRIBED EARLIER. ALSO CAN BE DESCRIBED AS RESIDUAL 'BRAIN FOG'.

5. GIVEN THE ABOVE, FROM THE PATIENT PERSPECTIVE, ANY NEW DIRECT ACTING ANTI-VIRAL TREATMENT MUST BE PREFERABLE TO THE SIDE EFFECTS AND POSSIBLE LONG TERM DAMAGE PATIENTS CAN EXPERIENCE WITH THE OLDER TREATMENTS

Please list any concerns you have about the treatment being appraised.

ON BEHALF OF THE PATIENTS I REPRESENT, THE ONLY CONCERN WOULD BE ANY SIDE EFFECTS NOT YET DISCOVERED DURING THIS APPRAISAL.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

THERE IS NO DIFFERENCE OF OPINION AMONG MY FELLOW PATIENTS OR COLLEAGUES.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

FROM MY OWN EXPERIENCE OF ADVANCED LIVER DISEASE, AND MY EXPERIENCE OF DAA TREATMENT, I WOULD SAY PATIENTS WITH

SERIOUS LIVER ISSUES OR NON-RESPONDERS TO PREVIOUS TREATMENTS WOULD BENEFIT MORE.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

I COULDN'T SAY THROUGH LACK OF DETAILED KNOWLEDGE OF THIS PARTICULAR TREATMENT.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes X☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations

from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

NO

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐X No

If yes, please explain what makes it significantly different from other treatments for the condition.

Is there anything else that you would like the Appraisal Committee to consider?

NO

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- QUALITY OF PATIENT EXPERIENCE ON TREATMENT
- LENGTH OF TREATMENT
- PATIENTS ABILITY TO FUNCTION DURING TREATMENT
- RESIDUAL SIDE EFFECTS WITH OLDER TREATMENTS
- LONG TERM DAMAGE TO PATIENTS ON OLD TREATMENTS THAT COULD REDUCE THEIR ABILITY TO CONTRIBUTE TO SOCIETY AND CAUSE FURTHER COST TO THE NHS IN THE FUTURE.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

As a regular member of an active and well attended support group for people living with hepatitis C, or going through treatment, I have found the experience of living with this disease is pretty much mirrored by most patients I come into contact with. So I offer this expanded statement to illustrate the issues patients experience whilst waiting for or going through treatment.

Background.

I am now [redacted], I was [redacted] when diagnosed with Hepatitis C after collapsing with end-stage liver disease while travelling in South East Asia in [redacted].

I am confident my hep c came through donating blood in Persia, Afghanistan or Pakistan, or dentistry/shaving in India during a trip I made between [redacted] to [redacted].

Therefore, assuming I caught the virus on that trip, and hearing my consultant's view on how long it would have taken the virus to do the amount of damage it did to my liver, I now believe I had this virus undetected for 35 years before I collapsed in Bali on [redacted].

Looking back, this would mean I already had hepatitis C when I first met my wife in [redacted], when I fathered 3 children between [redacted] and [redacted], and all the way through my career as a senior manager in [redacted].

Diagnosis.

My diagnosis came as a complete shock, at the time I didn't know anything about hepatitis C. I was fully vaccinated against A + B, plus typhoid and every other disease I needed protection against to travel. But I knew nothing about this strain of hepatitis.

My diagnosis in Bali revealed the following symptoms in addition to hepatitis C:

Decompensated liver cirrhosis
Chronic liver disease
Hematemesis-Melena
A Hiatal hernia
Reflux oesophagitis
A polypoid lesion on the fundic gaster
Portal hypertensive gastropathy
Erosive gastritis

It took a long time for my brain to compute this all happened to me as a direct result of carrying this virus undiagnosed for so long. From then on, the uncertainty about what was going to happen to me was a constant companion for 4 years, and at times put a great strain on my natural optimism for a full recovery, and also on my family and close friends.

From a patient perspective, this is a long time for anyone to spend in limbo, especially now that more effective Direct Acting Anti-viral drugs are available.

Living with the condition.

I regard the time spent between diagnosis in [redacted] and my cure in [redacted] as a frustratingly slow journey that was taken with my life completely on hold. A journey from darkness to light, so to speak.

After diagnosis I read all I could about the disease, which led me to consider very carefully what I put into my body and asked my liver to deal with. So no alcohol from that day to this (or ever again), juicing fresh fruit and vegetables at least once per day, cutting out fast food, convenience food, sweet food, fried food, tinned food, and drinking significantly more water than I ever used to, in the effort to help my liver recover from its hep c attack.

But my focus on getting well was being constantly compromised by prolonged spells of insomnia, anaemia, nausea, cramps, pruritus, headaches, confusion (brain fog) and lethargy, all symptoms of either the virus and/or the prescription drugs I was taking for the problems identified at diagnosis.

These symptoms had me reluctantly bed bound for the best part of 2 years while I also went through 2 unsuccessful attempts at treatment. In Sept [redacted] I was put on double therapy with Interferon and Ribavirin, but these 2 drugs made me very ill. The doctors stopped treatment 9 weeks into the 48 week course because my liver and kidney functions were collapsing with little response to my viral load.

This was a difficult time for my family as well, as the possibility of a quick cure and recovery slowly disappeared over the horizon. Once off the treatment drugs, I did start to feel a bit better as the toxicity of that drug combination slowly left my body, but I still remained with all the symptoms already mentioned.

One year later in Sept [redacted] another treatment option was introduced, Interferon and Ribavirin with Telaprevir added. I My body could only withstand this treatment for 21 days before being rushed to hospital, because my liver and kidneys were on the point of collapse with deranged electrolytes. I spent 8 days in hospital recovering from this episode and treatment was immediately stopped.

One element of this triple therapy programme required 20 grams of fat to be eaten with some of the pills every day, this was one of the most difficult things I've had to endure when you're already feeling nauseous with zero appetite. Again, recovery time from this treatment was frustratingly slow.

So ended 2 years of uncertainty with still no sign of a cure on the horizon. The new 'miracle' drugs I was hearing about were still somewhere in the future, awaiting NICE approval, and I was still suffering with insomnia, anaemia, nausea, cramps, pruritus and headaches.

In the meantime, regular blood tests continued to show high levels of AFP, but successive Ultra-sound, CT and MRI scans at my local [redacted] hospital couldn't locate a tumour. So I was referred to [redacted] in [redacted] and they found a tumour in my liver [redacted].

This led me into the transplant assessment programme, and inclusion on the waiting list in December [redacted]. I spent 24 hours on this list before being called in for transplant [redacted] [redacted] . 36 hours later the graft failed. Another 36 hours later a new liver was found and I was re-transplanted on Dec 11.

Again, the recovery from surgery was a slow process, obviously made worse by the ongoing symptoms of hepatitis c. As a patient in this scenario, not only is your own life on hold, but the mental strain on your family and friends over such a prolonged period of time is a source of stress.

It took my body about 12 months to recover from double transplant surgery, and a further 6 months waiting to see if my consultant could get me onto one of the several new drug trials [redacted] were involved with.

In March [redacted] my name was put forward for the Gilead solus 11 trial. At first I was told I had been accepted into one of the cohorts based on my Fibroscan result, which was 23 at that time. But within 2 weeks, my consultant had to inform me my name had been withdrawn, because the trial protocol had dictated the biopsy result as the determining factor, not the Fibroscan, and my biopsy result didn't qualify me. Naturally I was devastated.

Fortunately for me, my consultant fought very hard to get me back in and I started treatment on solus 11 in [redacted]. I started with a viral load of 1,450,000, this dropped to 457 on day 8, dropped again to 30 on day 15, and was undetectable at one month, and has stayed that way since. And there were virtually no side effects to cope with during this treatment throughout the 24-week programme.

Now I am fully recovered, going out socially, jogging again, enjoying family, friends and holidays. I am also working with the charity Liver4Life [redacted], and volunteering at the [redacted] support group [redacted]. In this group we offer information and advice to anyone who has hep c, is going through treatment, or just wants to know more about the disease.

Although I remained optimistic about my chances throughout, this was a scary way to live your life when you knew new drugs were available with a much better chance of cure.

Summary

At the moment, it is not easy telling patients who are living with hep c there is a waiting list for these new treatments, and that if their liver is currently working well, then their chance of early treatment is very much reduced.

I regard myself as a stable and balanced individual with no 'issues' to distract me during my treatment attempts and recovery. But many of the patients I come into contact with in our support group work are recovering substance abusers, the reasons for their substance abuse often based in childhood experiences of either abandonment, or mental, physical or sexual abuse, and drugs and/or alcohol became their escape.

As a support group volunteer trying to give something back to my community in return for the excellent care and compassion I received and continue to receive within the NHS, explaining to patients why they can't have these new treatments is a hard sell, particularly when I have experienced the major difference between the old and new.

The potential cost to the NHS further down the line for not curing patients today doesn't bear thinking about with liver disease on the rise.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Sofosbuvir in combination with velpatasvir for treating chronic hepatitis C

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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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
Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Manuela Joore acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Xavier Pouwels, Anoukh van Giessen, Nigel Armstrong and Ching-Yun Wei acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Regina Leadley acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Kate Misso critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

2D	Ombitasvir–paritaprevir–ritonavir
3D	Ombitasvir–paritaprevir–ritonavir with dasabuvir
3D/RBV	Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin
AASLD	American Association for the Study of Liver Diseases
AE	Adverse Events
ART	Antiretroviral treatment
BASL	British Association for the Study of Liver
BHIVA	British HIV Association
BI	Budget impact
BIC	Bayesian information criterion
BOC	Boceprevir
BOC/PR	Boceprevir in combination with pegylated-interferon alfa and ribavirin
BORR	Best overall response rate
BSC	Best supportive care
C	Cirrhotic
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CHC	Chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic kidney disease
CMU	Commercial medicines unit
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSR	Clinical study report
CUA	Cost utility analysis
DAA	Direct-acting antivirals
DAE	Discontinuation due to adverse events
DCV	Daclatasvir
DCV/PR	Daclatasvir in combination with pegylated-interferon alfa and ribavirin
DCV/SOF	Daclatasvir in combination with sofosbuvir
DCV/SOF/RBV	Daclatasvir in combination with sofosbuvir, with ribavirin
DoH	Department of Health
EASL	European Association for the Study of Liver
ECG	Electrocardiogram
EMA	European Medicines Agency
eRVR	Extended rapid viral response
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
EQ-5D-5L	European Quality of Life-5 Dimensions, five-level scale
ERG	Evidence Review Group
ESRD	End stage renal disease
EUR	Erasmus University Rotterdam
EVR	Early viral response
FAS	Full analysis set
FDA	Food and Drug Administration
5-FU	5-Fluorouracil
GT	Genotype
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma

HCV	Hepatitis C virus
HIV/HIV-1	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
IC	Indirect Comparison
ICD	International Classification of Diseases
ICER	Incremental Cost-effectiveness Ratio
ICTRP	International Clinical Trials Registry Platform
IFN	Interferon
ISPOR	International Society for Pharmacoecomics and Outcomes Research
ITT	Intention to Treat
IU	International unit
IV	Intravenous
KSR	Kleijnen Systematic Reviews
LDV	Ledipasvir
LDV/SOF	Ledipasvir in combination with sofosbuvir
LYS	Life Year Saved
MCMC	Markov Chain Monte Carlo
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MSD	Merck Sharp and Dohme
MTC	Mixed Treatment Comparison
NA	Not applicable
NC	Non-cirrhotic
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not Reported
NS5A	Non-structural protein 5A
OAE	Overall adverse events
OS	Overall survival
OST	Opiate substitution therapy
P	Pegylated-interferon alfa
PCR	Polymerase chain reaction
PR	Pegylated-interferon alfa in combination with ribavirin
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
PWIDs	People who inject drugs
QALY(s)	Quality-adjusted Life Year(s)
QoL	Quality of life
RAVs	Resistance-associated variants
RBV	Ribavirin
RCGP	Royal College of General Practitioners
RCT	Randomised Controlled Trial
RNA	Ribonucleic acid
RR	Relative Risk; Risk Ratio
SAE	Serious Adverse Events
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard deviation
SF-36	Short form 36

SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMV	Simeprevir
SMV/PR	Simeprevir in combination with pegylated-interferon alfa and ribavirin
SOF	Sofosbuvir
SOF/RBV	Sofosbuvir in combination with ribavirin
SOF/PR	Sofosbuvir in combination with ribavirin, with pegylated-interferon alfa
SOF/VEL	Sofosbuvir in combination with velpatasvir
SOF/VEL/RBV	Sofosbuvir in combination with velpatasvir, with ribavirin
SVR	Sustained virologic response
STA	Single Technology Appraisal
TBC	To Be Confirmed
TE	Treatment-experienced
TN	Treatment-naïve
TVR	Telaprevir
TVR/PR	Telaprevir in combination with pegylated-interferon alfa and ribavirin
UK	United Kingdom
UMC	University Medical Centre
WHO	World Health Organisation
WTP	Willingness to pay

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1. SUMMARY

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

The company's submission (CS) presents an evaluation of the clinical effectiveness and cost effectiveness of sofosbuvir-velpatasvir (SOF/VEL) for the treatment of chronic hepatitis C (CHC). The decision problem addressed by the CS was not completely in line with the final scope issued by the National Institute for Health and Care Excellence (NICE) with respect to the comparators. In particular, boceprevir and telaprevir are not included in the decision problem because these treatment regimens are no longer representative of current clinical practice according to the company.

The company's model does not include the development of resistance to SOF/VEL; the CS states that this was not considered in the economic model as this outcome does not impact the cost effectiveness of SOF/VEL, i.e. it has no impact on cost or QALYs.

1.2 Summary of clinical effectiveness evidence submitted by the company

The literature searches reported in the CS were well documented and easily reproducible. A good range of databases were searched, and additional searches of conference proceedings were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4.

Eighty-nine publications (reporting on 92 studies) were identified as meeting the eligibility criteria. Another 10 abstracts were identified from conference proceedings (eight additional studies plus one study reported in a full publication). Six of these publications/conference abstracts, representing seven studies, involved SOF/VEL. Three of these seven studies (ASTRAL-1 to 3) are reported by the company as the 'pivotal' RCTs.

The SOF/VEL trials included patients with all genotypes; treatment naïve and experienced patient populations; and patients with 'no cirrhosis and compensated cirrhosis'. In addition, ASTRAL-4 includes patients with decompensated cirrhosis.

SVR rates for SOF/VEL for 12 weeks were 98.1% for GT1a (ASTRAL-1), 99.2% for GT1b (ASTRAL-1), 99% to 100% for GT2 (ASTRAL-2 and 3), 95.3% for GT3 (ASTRAL-3), 100% for GT4 (ASTRAL-1), 97.1% for GT5 (ASTRAL-1), and 100% for GT6 (ASTRAL-1), infections. When split by cirrhosis status and previous treatment (naive or experienced), SVR rates were consistently above 95% for all genotypes, except for GT3. For patients with GT3, SVR rates were 98.2% for non-cirrhotic treatment-naive patients; 91.2% for non-cirrhotic treatment-experienced patients; 93.0% for cirrhotic treatment-naive patients; and 89.2% for cirrhotic treatment-experienced patients.

Health-related quality of life (HRQoL) questionnaires indicated no on-treatment decrements in HRQoL in SOF/VEL treated patients.

According to the company, SOF/VEL has a favourable safety and tolerability profile. No adverse drug reactions specific to SOF/VEL were identified, with the type, incidence and severity of AEs being comparable to placebo .

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

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

The conclusion from the SOF/VEL trials is that SOF/VEL has high SVR rates in all genotypes. In addition, SOF/VEL has a relative favourable safety and tolerability profile. Generally, the three

SOF/VEL trials were well conducted. However, ASTRAL-3 and 2 were open-label studies; therefore, care providers, participants and outcome assessors were not blinded to treatment allocation. In addition, in ASTRAL-3 there was a greater number of dropouts in the SOF/RBV treatment arm than in the intervention arm (n=21, vs. n=2 in SOF/VEL arm). Both issues mean that these trials are at a higher risk of bias.

The company attempted to perform a network meta-analysis (NMA) for comparator data, but decided that the results of the NMA were not considered to be robust or credible for use in the economic model. Instead, the company selected one SVR rate from individual arms from included studies for each population/intervention. The critique of the ERG to this approach is threefold:

1. The company selected one source for each intervention and population. Choices were often arbitrary and selecting results from a single arm of a study means that results are open to all the risks of bias associated with observational studies.
2. SVR rates are selected from a pool of RCTs retrieved through the company's original search. However, other study designs should have been included in the searches (uncontrolled studies, case series, etc.) because data are taken from individual study arms.
3. Sometimes multiple SVR rates are presented within a study; the choice for one particular SVR rate within a study is arbitrary again.

1.4 Summary of cost effectiveness submitted evidence by the company

The company developed a de novo health state transition model to assess the cost effectiveness of SOF/VEL compared to various comparators in patients with HCV. These patients are defined by HCV genotype, previous treatment, cirrhosis state, and interferon (IFN) eligibility. The comparators differ per subgroup. The comparators BOC and TVR were listed in the scope but excluded from the analyses by the company because these regimens are no longer deemed representative for current UK clinical practice. A National Health Service (NHS) and Personal and Social Services (PSS) perspective was adopted with a lifetime time horizon. Discount rates used for costs and quality-adjusted life years (QALYs) were 3.5%. The time horizon was until patients reach 100 years of age (in fact lifetime), and the cycle length was variable.

Patients in the model may be in a non-cirrhotic, compensated cirrhosis or decompensated cirrhosis state at model entry. From decompensated cirrhosis, patients may progress to a liver transplant (tunnel) state and post liver transplant state. From both cirrhosis states patients can progress to the hepatocellular carcinoma (HCC) state. Excess mortality is accounted for in the decompensated cirrhosis, liver transplant and HCC states. After active treatment, patients in the non-cirrhotic and (de)compensated cirrhosis states may achieve SVR. Patients in the non-cirrhotic SVR state are considered cured and will not become symptomatic again. All patients experience a background mortality risk, except when on treatment and during the period between the end of treatment and SVR assessment.

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 Vera-Llonch 2013 et al. and applied to the non-cirrhotic, cirrhotic and decompensated cirrhosis health states when patients had achieved a SVR.

Costs for SOF/VEL and comparator treatments were used in the cost effectiveness analysis. Besides drug acquisition costs, costs for monitoring and follow-up, costs associated with adverse events, and costs related to health states were included in the cost effectiveness analysis. These were all based on previous studies.

The company performed internal and external validation, but no cross validation.

For a willingness to pay of £20,000 and £30,000, SOF/VEL was cost effective compared to most comparators. SOF/VEL (anticipated list price) was not cost effective compared to LDV/SOF (GT1 TN non-cirrhotic) and 2D/RBV (GT4 TN non-cirrhotic and GT4 TE non-cirrhotic). Moreover, based on a willingness to pay of £20,000 and £30,000, SOF/VEL (discounted price) was not cost effective compared to PR (GT2 TN non-cirrhotic). For the different subpopulations, the probability that SOF/VEL is cost effective ranged between 18%-93% for a threshold value of £20,000 and between 23%-95% for a threshold value of £30,000.

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

Patients who are post-liver transplant were not modelled separately due to a lack of data, and the ERG acknowledges that evidence on this population is scarce.

The model structure is conceptually similar to the models that were submitted in previous assessments of HCV treatment. According to the ERG, the model structure reasonably reflects the key elements of HCV disease, although some simplifications were made. For example, not including reinfection in the model structure favours all active treatments. The ERG thinks a structure that allows for reinfection is more in line with the disease pathway and will hence be used in the ERG's analyses.

Single arms from RCTs were used to estimate comparative effectiveness, as driven by SVR, discontinuation and AE rates for SOF/VEL and its comparators. The ERG has concerns on the validity of this naïve comparison of single study arms, which is not in line with evidence synthesis best practices and susceptible to bias (i.e. prone to similar biases as observational comparisons).

A targeted literature review was performed to obtain genotype-specific transition probabilities from the non-cirrhotic to the compensated cirrhotic health states. The ERG considered the targeted search to identify these transition probabilities as inadequate. Other disease progression related transition probabilities were taken from literature sources and were independent of treatment or GT status. In addition, the ERG discovered calculation errors in the transition probabilities found in the literature, which were corrected in the ERG additional analyses.

SF-6D utilities from the ASTRAL trials could have been used by the company in their cost effectiveness analysis instead of the utilities from the literature. The ERG has concerns on the estimates of on-treatment utility increments and decrements. The ERG also questioned the use of an SVR utility increment for the decompensated cirrhosis health state. This utility increment was removed in the ERG additional analyses.

The ERG thinks that the cost effectiveness analysis based on list prices may not reflect the actual value for money of the HCV treatments.

The ERG has concerns on the validation status of the cost effectiveness analysis. The Excel model suffered from a lack of transparency, and mistakes were detected in the technical implementation of

the model. No details were given concerning the external validation and cross validation was completely lacking.

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

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. The CS and response to clarification provided sufficient details for the ERG to appraise the searches. Efforts were made to identify e-Pub ahead of print publications on PubMed for the clinical effectiveness searches. Additional searches were carried out for conference abstracts.

The company's submitted evidence on clinical effectiveness broadly covered the final scope set out by NICE. The review of SOF/VEL trials included all relevant trials in which SOF/VEL had been used. Reviews for other treatments were likely to have identified the majority of trials of other relevant treatments. The submission covers the key clinical outcomes, including SVR rates, adverse events and mortality.

The economic model structure reflects the main aspects of the chronic HCV disease, meets the NICE reference case to a large extent and is mostly in line with the decision problem specified in the scope.

1.6.2 Weaknesses and areas of uncertainty

Clinical effectiveness searches were limited by date from 2006, however a key trial published in 2004 (Zeuzem et al., 2004) was included in the NMA. It was unclear how this study was found. The ERG noted the clinical effectiveness Embase RCT search used extensive focused Emtree indexing terms which may have adversely affected recall of the search strategy. Searches were not conducted to identify non-RCT evidence. The ERG was concerned that specific adverse events searches without the restriction of a study design filter were not conducted; this is not in line with current best practice. Cost effectiveness searches of the HTA and NHS EED database could have been less restrictive.

The main concern regarding clinical effectiveness is that comparator data (for SVR12 and AEs) were taken from single arms of randomised controlled trials (RCTs). Overall, the justifications provided by the company for each selected SVR rate seem valid. However, it would be quite easy to provide an equally valid justification for most of the alternative sources. Therefore, the main problem with this method of selecting inputs for the economic model still stands: using only one source for each intervention and population increases the chance of bias and cherry-picking.

The cost effectiveness analyses were based on the treatment effectiveness data, and as a result all health economic analyses suffered from the uncertainty of evidence synthesis, as well.

Furthermore, some analyses were conducted on list prices, which may not reflect the actual value for money of the treatments.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG raised a number of issues. Not all of these issues could be quantified and included in the ERG base-case. This includes the following:

- Arbitrary selection and single arm comparisons of SVR rates (one of the main drivers of the model),

- Lack of face/internal validity of the model (e.g. assuming a year with 48 weeks, incorporating a period without any disease progression and mortality, not adjusting the liver transplant tunnel for shorter cycle lengths, not incorporating effects on the population infection rate),
- Simplifications in the model structure (i.e. not distinguishing between mild and moderate cirrhosis),
- Not systematically identifying sources for all transition probabilities in the model,
- Not using the Health Related Quality of Life (HRQOL) evidence collected with the SF36 in the ASTRAL trials in the model,
- Not providing sufficient justifications for (sources used for) the on-treatment utility increments.

The ERG mainly has concerns on the validity of the naïve comparison of single study arms, which is not in line with the evidence synthesis best practices and susceptible to bias. It raises the question whether the differences in SVR rates between the comparators are true differences between the comparators or whether these differences are driven by differences between the studies used to obtain SVR rates (e.g. difference in study population, context, design). Therefore, any analysis (both by the company and ERG) should be interpreted with extreme caution.

It should be noted that not all comparators were included in the model received by the ERG (see Table 6.1 for more details), hence the ERG could not calculate the results for these comparators or was forced to make assumptions for this purpose (e.g. assuming the results for DCV/SOF/RBV are equal to DCV/SOF for GT1 (CC)). In particular the inability to calculate results for DCV/PR was considered an issue, as this resulted in an ICER larger than £30,000 in the company's analysis compared with SOF/VEL.
The ERG created a new base-case by correcting calculation errors in transition probabilities, incorporating reinfection, and removing the SVR utility increment for the decompensated cirrhosis health state. The results of the ERG base-case are similar to the CS base-case with regards compared to which comparators SOF/VEL is not cost-effective (only SOF/PR was added to this list in the ERG base-case). For a willingness to pay of £20,000 and £30,000, in the ERG base case SOF/VEL (anticipated list price) was not cost effective compared to:

- 3D (GT1 TN and TE non-cirrhotic);
- LDV/SOF (GT1 TN non-cirrhotic, GT4 TN and TE cirrhotic);
- 2D/RBV (GT4 TN and TE non-cirrhotic);
- 3D/RBV (GT1 TN and TE non-cirrhotic);
- PR (GT3 TN non-cirrhotic) and;
- SOF/PR (GT3 TE non-cirrhotic).

These results are similar to the CS base-case, as SOF/VEL is not cost effective in comparison to the same comparators (only SOF/PR in GT3 treatment experienced non-cirrhotic patients was added). As mentioned above, for DCV/PR (GT4 TN non-cirrhotic), no results could be calculated by the ERG. SOF/VEL (discounted price) was not cost effective compared to PR (GT2 TN non-cirrhotic). However, the results of these additional analyses by the ERG should be interpreted with caution, as they were based on treatment effectiveness parameters that were based on questionable assumptions/methods.

2. BACKGROUND

This report provides a review of the evidence submitted by Gilead Sciences International Ltd in support of Sofosbuvir/velpatasvir (SOF/VEL): (tradename Epclusa®) for the treatment of chronic hepatitis C for both treatment naïve and previously treated patients.[1] The background section of the report by the ERG outlines and critiques the company's description of the underlying health problem and the overview of current service provision.[1]

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

The underlying health problem of this appraisal is hepatitis C described in the company submission (CS) as a 'progressive infectious disease caused by HCV infecting the liver; the main route of transmission is through exposure to infected blood'.[1]

ERG comment: The CS states the main route of transmission is through exposure to infected blood and provides a 2006 publication as reference.[2] The ERG would suggest there is more recent information as the implementation of the blood product safer injections practices in 2010 has reduced the transmission of HCV infection through contaminated blood products, syringes, needles and/or medical equipment in developed countries.[3] The primary source of new infections is now among people who inject drugs (PWID) through needle sharing. In England this is estimated to be 90%.[4] The company states that of the six major genotypes 'In England sentinel surveillance data from 2010 to 2014 show GT1 (47%) and GT3 (44%) predominating'.

The CS uses 2015 report on 'Hepatitis C in the UK as a reference for epidemiology of HCV genotype.[5] The ERG considers this a reliable source.

The company appraisal, as per the NICE scope,[6] is related to patients with chronic hepatitis C which the company states occurs in 'up to 75-85% of those with acute HCV infection'.[1] The risks of hepatitis C, when untreated, are outlined in the CS. The company further states that 10-20% of patients with CHC will go on to develop cirrhosis over a 20-year period and once cirrhosis is established, HCC develops at a rate of 1-4% per year'.[1]

ERG comment: The figures quoted are taken from 'The natural history of hepatitis C virus infection and is considered by the ERG to be a reliable source.[2]

CHC is associated with considerable burden to patient and society. The CS states that there are approximately 214,000 people in the UK chronically infected with HCV including 160,000 in England.[1] The CS states that the incidence of HCV-related liver disease has risen considerably in recent decades. Furthermore, as transmission among risk groups remains prominent and significant numbers remain undiagnosed and untreated; this burden is expected to rise. Similarly, the number of registrations for liver transplants in the UK as a result of hepatitis C-related cirrhosis has increased by almost 300% from 45 cases in 1996 to 175 in 2014. Deaths resulting from HCV-related end-stage liver disease or HCC increased by more than 300% between 1996 and 2014 in England.

The CS describes how CHC is associated with reduced HRQoL. Activities of daily living can be impaired and work productivity can be affected. Patients also have to deal with the social stigma associated with CHC, irrespective of the method of HCV acquisition or socioeconomic status.

ERG comment: The CS cites 'Hepatitis C in the UK' as a reference to support statements on epidemiology.[5] This is considered a reliable source by the ERG. The increased incidence of HCV-

related liver disease, need for liver transplants and deaths as a result of HCV-related end stage liver disease are clearly outlined. The burden to patient, carers and society are clearly described and supported with valid references.

The CS states that liver disease is estimated to cost the NHS in excess of £500 million per year, a figure that is rising by 10% every year. The costs of hospital admissions and liver transplants related to HCV are also presented.

ERG comment: It is important to clarify that the figure of £500 million includes all liver disease not just liver disease as a result of HCV.

2.2 Critique of company's overview of current service provision

The CS states that 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 2015 guidelines[7] and NICE technology appraisals (TA75, 106, 200, 252, 253, 330, 331, 361, 363, 364, and 365).[8-18] It further explains the influence of HCV genotype, the severity of liver disease – absence or presence of cirrhosis, and the stage of cirrhosis (compensated or decompensated) – and whether a patient has received treatment for the condition previously – CHC treatment-naïve or treatment-experienced on treatment efficacy and choice and cites EASL recommendations as a supporting reference.[7]

The CS summarises current NICE recommendations from technology appraisals for CHC treatments are summarised in Table 4 and Table 5 of their submission.[1] They indicate that based on these recommendations it is clear that some patient groups, such as those with GT1 and GT4 infection are reasonably well served with several treatment choices. However, for other groups such as those with GT3 infection, treatment choices are still limited.

The CS presents the case for SOF/VEL as the first pan-genotypic single tablet regimen (STR) for the treatment of CHC, providing a simple, all-oral, once-daily, Pegylated-interferon alfa (P)- and RBV-free treatment option for all adult patients, including those with compensated cirrhosis. They further state the addition of RBV to the regimen, allows high cure rates to be achieved in patients with decompensated cirrhosis. SOF/VEL is positioned as a simple, highly effective and well tolerated treatment option for all patients with CHC, irrespective of genotype, severity of liver disease or prior treatment experience. Specifically it will also provide a much-needed option in those groups that are seen to be the hardest to treat and with the highest unmet need, such as those:

- with GT3 infection
- with compensated and decompensated cirrhosis
- who are ineligible for P
- who are ineligible for RBV
- who are CHC treatment-experienced

ERG comment: The company outlines the need for further treatment options for CHC and outlines the positioning of SOF/VEL as an option for difficult to treat populations and those with the highest unmet need namely GT3 population, CHC treatment inexperienced and those ineligible for P and RBV. The limitations associated with P and RBV namely low SVR rates, side effects, contraindications, need for safety and efficacy monitoring, high discontinuation rates due to AE, long duration of treatment and weekly subcutaneous injections (P) or multiple tablets daily (RBV) are listed in section 3.7 of the CS support the case for SOF/VEL.[1] The CS states there is additional morbidity associated with this GT3 but do not support this statement with a reference. All additional

statements regarding higher rates of fibrosis development, development of HCC and all-cause mortality compared to other genotypes are fully supported.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comments
Population	Adults with CHC • Who have not had treatment for CHC before (treatment-naive) • Who have had treatment for CHC before (treatment-experienced)	As per final scope	This is in accordance with the scope.
Intervention	SOF/VEL	As per anticipated marketing authorisation • SOF/VEL 12 weeks for all patients without cirrhosis or compensated cirrhosis, including those with HIV co-infection. • SOF/VEL/RBV 12 weeks for patients with decompensated cirrhosis	This is in accordance with the scope.
Comparator(s)	• Best supportive care (watchful waiting) (GT1-6) • BOC/PR (for GT1 only) • DCV/PR (for specific people with GT4; as recommended by NICE) • DCV/SOF±RBV (for specific people with GT1, 3 or 4; as recommended by NICE) • LDV/SOF (for specific people with GT1 or 4; as recommended by NICE) • 2D±RBV or 3D±RBV (for GT1 or 4) • PR (for GT1-6) • SMV/PR (for GT1 or 4) • SOF/PR or SOF/RBV (for specific people with GT1-6; as recommended by NICE) • TVR/PR (for GT1 only)	As per final scope, with the following exceptions: • All active treatments are included in line with NICE recommendations from technology appraisals • "Best supportive care" is defined as no treatment in this submission ○ "No treatment" modelled in line with previous submissions and in the context of Public Health England data that shows very poor linkage to the care of patients who are diagnosed but not treated (i.e. how "watchful waiting" in the UK context doesn't work with this patient population) • BOC and TVR included by extrapolating from findings for SOF/VEL versus SMV/PR ○ As discussed at the NICE decision problem meeting, BOC and TVR are rarely used in	Mostly in line with the final scope, albeit with some discrepancies (see Section 3.3). The company notes that "best supportive care" is defined as no treatment in their submission. In addition, boceprevir and telaprevir are not included in the decision problem because these treatment regimens are no longer representative of current clinical practice according to the company.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comments
		the NHS, having been superseded by SMV. Neither BOC nor TVR have been included in Gilead's economic modelling and the modelling approach taken was to extrapolate from the findings of SOF/VEL versus SMV/PR, an approach which NICE agreed was reasonable	
Outcomes	The outcome measures to be considered include: • SVR • Development of resistance to treatment • Mortality • Adverse effects of treatment • HRQoL	As per final scope except: • The development of resistance to SOF/VEL is discussed only in Section 4 as this outcome does not impact the cost-effectiveness of SOF/VEL, i.e. it has not impact on cost or QALYs	In line with the final scope. The company states that the development of resistance to SOF/VEL was not considered in the economic model as this outcome does not impact the cost-effectiveness of SOF/VEL, i.e. it has no impact on cost or QALYs.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per final scope. The time horizon for the modelling is a lifetime.	In line with the final scope. The company's submitted model evaluates costs and health gains (reported as incremental costs per quality-adjusted life year) from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon.
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Genotype • Co-infection with HIV • People with and without cirrhosis • People who have received treatment before liver transplantation, and those who have	Evidence allowed subgroup analyses including: • Genotype • People with and without cirrhosis • People with decompensated cirrhosis	Separate subgroup analyses are not presented for patients who are co-infected with HIV, post-liver transplantation, and people who are intolerant to or ineligible for interferon treatment.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comments
	received it after liver transplantation • Response to previous treatment (non-response, partial response, relapsed) • People who are intolerant to or ineligible for IFN treatment		
Special considerations including issues related to equity or equality		CHC GT3 patients are characterised by a disproportionately higher number of patients from migrant backgrounds, which could potentially raise an equality issue if these people encounter greater difficulty in achieving access to SOF/VEL	

Source: Section 1.2 of the CS.[1]
Abbreviations: BOC, boceprevir; CHC, chronic hepatitis C; DCV, daclatasvir; DSV, dasabuvir; GT, genotype; HRQoL, health-related quality of life; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; Peg-IFN, pegylated-interferon alfa; PTV, paritaprevir; QALY, quality adjusted life year; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TVR, telaprevir; VEL, velpatasvir

3.1 Population

The patient population described in the final scope are: People with chronic hepatitis C: who have not had treatment for chronic hepatitis C before (treatment-naive) or who have had treatment for chronic hepatitis C before (treatment-experienced).

On 26 May 2016 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Epclusa, (sofosbuvir/velpatasvir) intended for the treatment of chronic hepatitis C in adults.[19]

The population is in line with the NICE scope.

3.2 Intervention

The intervention described in the final scope is sofosbuvir/velpatasvir. According to the CHMP, Epclusa is a fixed dose combination of two direct-acting antivirals, sofosbuvir and velpatasvir. It will be available as film-coated tablets (containing 400 mg sofosbuvir and 100 mg velpatasvir). The active metabolite of sofosbuvir is an inhibitor of the hepatitis C virus (HCV) NS5B RNA polymerase, while velpatasvir targets the NS5A protein of the virus.[19]

The SmPC specifies that sofosbuvir/velpatasvir is recommended for treatment of patients without cirrhosis and patients with compensated cirrhosis (SOF/VEL for 12 weeks), and for patients with decompensated cirrhosis (SOF/VEL/RBV for 12 weeks).[20]

3.3 Comparators

The comparators described in the final scope are as follows:

- best supportive care (BSC; watchful waiting) (genotypes 1-6)
- boceprevir in combination with pegylated-interferon alfa and ribavirin (BOC/PR; for genotype 1 only)
- daclatasvir in combination with pegylated-interferon alfa and ribavirin (DCV/PR; for specific people with genotype 4; as recommended by NICE)
- daclatasvir in combination with sofosbuvir, with or without ribavirin (DCV/SOF or DCV/SOF/RBV; for specific people with genotype 1, 3 or 4; as recommended by NICE)
- ledipasvir in combination with sofosbuvir (LDV/SOF; for specific people with genotype 1 or 4; as recommended by NICE)
- ombitasvir–paritaprevir–ritonavir with or without dasabuvir or ribavirin (2D, 3D, or 3D/RBV; for genotype 1 or 4)
- pegylated-interferon alfa in combination with ribavirin (PR; for genotypes 1- 6)
- simeprevir in combination with pegylated-interferon alfa and ribavirin (SMV/PR; for genotype 1 or 4)
- sofosbuvir in combination with ribavirin, with or without pegylated-interferon alfa (SOF/RBV or SOF/PR; for specific people with genotypes 1-6; as recommended by NICE)
- telaprevir in combination with pegylated-interferon alfa and ribavirin (TVR/PR; for genotype 1 only)

The company made the following changes:

- "best supportive care" is defined as no treatment.
- boceprevir (BOC) and telaprevir (TVR) are excluded from the decision problem as these treatment regimens are no longer deemed representative of current clinical practice.

ERG comment: The ERG's clinical expert agreed that indeed these two drugs were no longer used in clinical practice.

3.4 Outcomes

The CS[1] includes the following outcomes, all of which are specified in the final NICE scope[6]:

- SVR
- Mortality
- Adverse effects of treatment
- HRQoL

The CS does not include one of the outcomes specified in the NICE scope, that is, the development of resistance to sofosbuvir/velpatasvir, stating that this was not considered in the economic model as this outcome does not impact the cost effectiveness of SOF/VEL, i.e. it has no impact on cost or QALYs. Clinical advice received by the ERG suggests that this end point reflects treatment failure other than that from not taking pills. Given the high SVR rates this outcome may therefore be less relevant.

3.5 Other relevant factors

The decision problem addressed by the CS[1] includes consideration of the following subgroups, all of which were specified in the final NICE scope[21]:

- Genotype
- People with and without cirrhosis
- People with decompensated cirrhosis

Separate subgroup analyses are not presented for patients who are co-infected with HIV, post-liver transplantation, and people who are intolerant to or ineligible for interferon treatment.

Regarding special considerations including issues related to equity or equality, the submission the submission states that CHC GT3 patients are characterised by a disproportionately higher number of patients from migrant backgrounds, which could potentially raise an equality issue if these people encounter greater difficulty in achieving access to SOF/VEL.

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Clinical effectiveness

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies, was used to inform this critique.[22] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[23] The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of each search strategy can be found in Appendix 1.

The CS states that a systematic review was conducted to identify randomised clinical data from the published literature regarding the efficacy of SOF/VEL and comparators for the treatment of chronic hepatitis C (section 4.1). Searches were reported for MEDLINE, MEDLINE In-Process, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL), and were undertaken in December 2015. A supplementary search to identify e-Pubs ahead of print was also carried out during December 2015. A second Embase search was carried out to identify conference abstracts for the annual meetings of the Liver Meeting (American Association for the Study of Liver Diseases (AASLD)) and the European Association for the Study of the Liver (EASL) for the last two years (2014-2015). The Embase conference search was conducted in January 2016. These met the requirements detailed in the NICE guide to the methods of technology appraisal.[24]

Search strategies for the database searches were provided in the Appendix 3 of the CS[25] and were well reported and reproducible. The ERG noted that the PubMed search was included to identify e-Pub ahead of print records not yet available in MEDLINE via the Ovid database host. For the most part, the database searches were clearly structured and used combinations of index terms appropriate to the resource searched, free text and a number of synonyms for the condition, intervention and most of the comparators.

The company's searches of MEDLINE, MEDLINE In-Process, Embase, Cochrane and PubMed were restricted by date from 2006 to date of search. The ERG noted that in Section 4.10.3, the CS reported that one of the trials used to inform the NMA and to connect 'SOF12+VEL12' to the main network was published in 2004.[26] The CS reports that "This study was not identified in the systematic review because of the 2006 date cut off applied, but was deemed the most appropriate to complete the evidence network".

Given the need to include an earlier publication[26] missed by the clinical effectiveness searches, the ERG queried the rationale behind this restriction in the clarification letter.[27] The clarification response[28] presented the following rationale:

"We searched from 2006 onwards because we believe literature prior to this point would be dominated by interferon-based treatments, which are progressively becoming less relevant to UK clinical practice for the treatment of CHC. As such it was felt that literature from 2006 onwards was more likely to reflect current clinical practice and would be most informative."

The ERG did not consider the explanation provided in the clarification response sufficient to justify inclusion of a single earlier trial, and that failing to search for and screen other studies from 2004-

2006 may have introduced bias to the search and study selection processes. The ERG felt that the clinical effectiveness searches should have been conducted from 2004 to date, or without any date limitation, in order to ensure the results were comprehensive and objective.

The Embase RCT search included Emtree indexing within both the population and drug facets, where the indexing terms had been restricted to focus (RTF), i.e. only major Emtree indexing headings were retrieved. When these restrictions were queried, the justification given in the clarification response was that this approach had been adopted to compensate for Emtree over-indexing. The company reported assessing the impact of RTF by checking that all the included studies were picked up by the Embase strategy. Recent investigations have been conducted into the impact of using RTF in Emtree on overall search sensitivity and recall.[29, 30] Current recommendations for best practice advocate caution when considering introduction of RTF in the population facet of an Embase search. Furthermore, prudence is also recommended when considering Emtree RTF in more than two concepts,[29, 30] as the ERG noted in the CS clinical effectiveness search. The ERG considered the extensive use of RTF overly restrictive and potentially impairing recall of possibly relevant references. The ERG did not consider the company's method of retrospective assessment of recall adequately robust; the ERG's issue was not whether the search found the studies it had already found, concerns remained regarding the restricted strategy missing potentially relevant records that should have been screened but were not retrieved in the first place. The ERG acknowledges the difficulties resulting from over-indexing of Embase records, namely retrieval of high numbers of records, however the ERG did not consider the extensive implementation of RFT in the Embase search adequately sensitive for this systematic review.

Terms were used to limit results to randomised trials only. The host provider for each database was listed, and the specific date the searches were conducted were provided. The date spans for all searches were not included in the CS, however further details were provided following a clarification request.[27]

Indirect and mixed treatment comparisons

The clinical effectiveness searches reported in section 4.1 and Appendix 3 were used to inform the indirect and mixed treatment comparisons. As the searches included a facet of relevant comparators the ERG considered the searches fit for purpose, although the limitations noted in the clinical effectiveness searches also applied in this context.

Non-randomised and non-controlled evidence

No searches for non-randomised studies were reported.

Adverse events

The CS[1] stated that the four ASTRAL trials[31-33] provided safety evidence for SOF/VEL. Specific AE searches were not performed. When the ERG queried this omission, the clarification response[28] stated that the clinical effectiveness searches reported in section 4.1 and Appendix 3 were used to identify studies reporting safety data. The searches used for the clinical effectiveness section (4.1) were described as being used to identify the efficacy, tolerability and safety of the specified treatment and comparators for chronic hepatitis C. Guidance by the Centre for Reviews and Dissemination (CRD)[34] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. The ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits used. Unfortunately the ERG was unable to undertake

independent AE searches and review the results within the STA timeline, as this would be outside of the ERG remit.

Summary of searching

The searches in the CS were well documented and easily reproducible; searches were carried out in line with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4.[24] The ERG noted a date limit of 2006 was applied, however one study from 2004 had been included. Separate adverse events and non-RCT searches were not conducted.

4.1.2 Inclusion criteria

The company used one set of inclusion criteria for intervention trials and comparator trials. The inclusion criteria are outlined in Table 4.1 (see CS Table 9, page 61).

Table 4.1: Eligibility criteria used in search strategy

PICOS	Inclusion criteria
Population	Adult patients infected by HCV with genotypes 1–6 HCV, treatment-naïve or treatment-experienced, HIV co-infected, recurrent HCV, liver transplant patients
Interventions and comparators	Pegylated interferon alfa, ribavirin, telaprevir, boceprevir, simeprevir, daclatasvir, asunaprevir,† sofosbuvir, faldaprevir,† ledipasvir, ombitasvir, paritaprevir, ritonavir, dasabuvir, grazoprevir, elbasvir, velpatasvir, placebo, no treatment Only combinations with and comparisons between list drugs were included Only licenced doses, or doses expected to be licenced, were included
Outcomes	SVR12/24, RVR, EVR, eRVR, EOT, safety outcomes and mortality
Study design	Randomised trials: Phase II and III clinical trials

Source: CS Table 9, page 61

EOT, end of treatment; eRVR, extended rapid virologic response; EVR, early virologic response; RVR, rapid virologic response; SVR, sustained virologic response.

†These comparators were included in the initial protocol but subsequently removed at full paper review stage as marketing authorisation applications for these products is not being pursued in this indication.

eRVR defined as undetectable HCV RNA levels at weeks 4 and 12 of treatment; EVR defined as undetectable HCV RNA level at week 12 of treatment; RVR defined as undetectable HCV RNA level at week 4 of treatment; SVR12/24 defined as undetectable serum HCV RNA 12/24 weeks after the end of treatment

ERG comment: These inclusion criteria match the decision problem set out within the final NICE scope[6] in terms of the population and the intervention. At full paper review stage, the dosing strategies of the treatment arms were assessed. Only doses that are currently licenced, or expected to be licenced were included. A major limitation is that there is a language restriction: only English language publications are included.

The company did not mention in the eligibility criteria that a 2006 date cut-off was applied. This is only mentioned on page 107 of the CS and in Appendix 3 (search strategy). It is not clear why this date cut-off was used; especially given that an additional study (Zeuzem et al., 2004[26]) had to be included in order complete the evidence network (see also section 4.1.1 of this report).

The inclusion criteria state that only randomised trials were included. This is appropriate for a normal network met-analysis (NMA). However, the company decided that a normal NMA has too many

limitations and performed a naive comparison, using individual arms of studies instead. For such an analysis limiting the inclusion criteria to randomised trials only makes no sense. Therefore, for the naive comparison many relevant studies may have been missed.

It is not stated how many reviewers conducted the study selection process (see CS page 60); therefore, errors in study selection cannot be ruled out. It is generally considered good practice to perform each stage of the systematic review process (screening titles and abstracts, full paper selection, data extraction and risk of bias assessment) by two independent reviewers. The study selection process was provided in a flow diagram of study selection (see CS Figure 2, page 62) that indicates that 89 publications (reporting on 92 studies) were identified as meeting the eligibility criteria. Another 10 abstracts were identified from conference proceedings (eight additional studies plus one study reported in a full publication). Six of these publications/conference abstracts, representing seven studies, involved SOF/VEL.[31-33, 35-37] Three of these seven studies (ASTRAL-1 to 3) are reported by the company as the 'pivotal' RCTs and are presented in Table 4.2.

The remaining four studies are described by the company as 'randomised, non-controlled studies'.[32, 33, 35-37] They are in fact studies without a control group. ASTRAL-4 is a randomised study in adult patients with confirmed CHC of any genotype with decompensated cirrhosis (confirmed CPT class B at screening) comparing three arms: SOF/VEL for 12 weeks, SOF/VEL/RBV for 12 weeks, and SOF/VEL for 24 weeks.[33, 38]

The other three studies (Pianko et al, 2015,[36] Everson et al, 2015[35], ELECTRON-2[37]) are excluded from further discussion (see CS, page 152).

Finally, ASTRAL-5 is mentioned in the submission but not listed among these included studies.[39] ASTRAL-5 is an ongoing study in patients co-infected with HCV and HIV; preliminary data were presented at EASL in April 2016. This study is briefly described in section 4.11.8 of the CS.

Table 4.2: Studies involving SOF/VEL

Trial no. (acronym)	Intervention(s)	Comparator(s)	Population	Primary study refs.
Pivotal Phase III RCTs				
GS-US-342-1140 (ASTRAL-3)	SOF/VEL for 12 weeks	SOF/RBV for 24 weeks	CHC GT3 Treatment-naïve and treatment-experienced No cirrhosis and compensated cirrhosis	Foster et al, 2015[31] Supporting information from CSR[40]
GS-US-342-1139 (ASTRAL-2)	SOF/VEL for 12 weeks	SOF/RBV for 12 weeks	CHC GT2 Treatment-naïve and treatment-experienced No cirrhosis and compensated cirrhosis	Foster et al, 2015[31] Supporting information from CSR[41]
GS-US-342-1138 (ASTRAL-1)	SOF/VEL for 12 weeks	Placebo for 12 weeks	CHC GT1, GT2, GT4, GT5, GT6 Treatment-naïve and treatment-experienced No cirrhosis and compensated cirrhosis	Feld et al, 2015[32] Supporting information from CSR[21]
Non-randomised and non-controlled studies				
GS-US-342-1137 (ASTRAL-4)	SOF/VEL for 12 weeks SOF/VEL/RBV for 12 weeks SOF/VEL for 24 weeks	NA	HCV GT1-6 Treatment-naïve and treatment-experienced Decompensated cirrhosis (classified as CPT class B)	Curry et al, 2015[42] Supporting information from CSR[38]
ASTRAL-5 (ongoing)	SOF/VEL for 12 weeks	NA	HCV genotypes 1–6 and HIV Treatment naïve or experienced No cirrhosis and compensated cirrhosis	Wyles et al, 2016[39]
Non-randomised and non-controlled studies excluded from further discussion				
NCT01909804 (Pianko et al)	SOF 400mg / VEL 25mg for 12 weeks SOF 400mg / VEL 25mg / RBV for 12 weeks SOF 400mg / VEL 100mg for 12 weeks SOF 400mg / VEL 100mg / RBV for 12 weeks	NA	HCV GT1 and GT3 Treatment-experienced No cirrhosis and compensated cirrhosis	Pianko et al, 2015[36]

Trial no. (acronym)	Intervention(s)	Comparator(s)	Population	Primary study refs.
NCT01858766 (Everson et al)	SOF 400mg / VEL 25mg for 12 weeks SOF 400mg / VEL 25mg / RBV for 12 weeks SOF 400mg / VEL 100mg for 12 weeks SOF 400mg / VEL 100mg / RBV for 12 weeks	NA	HCV GT1-6 Treatment-naïve No cirrhosis	Everson et al, 2015[35]
ELECTRON-2	SOF 400mg / VEL 25mg for 8 weeks SOF 400mg / VEL 25mg / RBV for 8 weeks SOF 400mg / VEL 100mg for 8 weeks SOF 400mg / VEL 100mg / RBV for 8 weeks	NA	HCV GT3 Treatment-naïve No cirrhosis	Gane et al, AASLD 2014[37]

Source: CS, Table 11, page 64, Table 43, page 151, and Table 44, page 152.

CHC, chronic hepatitis C; CPT, Child-Pugh-Turcotte; CSR, clinical study report; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NA, Not applicable; RBV, ribavirin; RCT, randomised controlled trial; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

4.1.3 Critique of data extraction

For HRQoL studies, data extraction was performed independently by two reviewers (CS, Appendix 16.7, page 120); and for cost studies the data extraction process was not described (CS, Appendix 17). For effective studies it is not stated how many reviewers were involved in the data extraction process.

4.1.4 Quality assessment

Table 23 in section 4.6 of the CS[1] provided an overview of the quality assessment of the SOF/VEL RCTs. A complete quality assessment with supporting evidence of how the quality criteria were met was provided in Appendix 4.[25]

Table 4.3: Comparison of quality assessment of relevant RCTs by CS and ERG

	GS-US-342-1140 (ASTRAL-3) CHC GT3		GS-US-342-1139 (ASTRAL-2) CHC GT2		GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6	
	CS	**ERG**	**CS**	**ERG**	**CS**	**ERG**
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No	No	No	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	Yes	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	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	Yes	Yes

ERG comment: The ERG can find no reference to the criteria used to assess study quality e.g. the Cochrane Collaboration's tool for assessing risk of bias in randomised trials or similar.[43]

Appendix 4 of the CS states that in Astral-3 an Interactive Web Response System (IWRS) was employed to manage subject randomisation and treatment assignment. Demographic and baseline clinical characteristics were generally well balanced. As the study was open-label, care providers, participants and outcome assessors were not blinded to treatment allocation. There were greater number of dropouts in SOF/RBV treatment arm (n=21, vs. n=2 in SOF/VEL arm) and reasons for drop outs were provided. Authors of the CS state this difference may have been expected due to the use of RBV and the longer treatment duration in the SOF/RBV arm. Modified intention to treat (ITT) was used. The analyses assessed the patients that were randomised and received at least one dose of study drug (FAS) and appropriate methods were used to account for missing data.[25]

ERG comment: The ERG would suggest there were unexpected imbalances in dropouts between groups when comparing discontinuations of treatment. In contrast the CS states that the imbalances in dropouts are not unexpected and suggests the longer duration of treatment as a reason for the imbalance. The ERG suggests this is unlikely as the intervention is not one which is difficult or unpleasant to administer. The ERG cites Figure S2 in the supplementary appendix which illustrates that of the 280 randomised to receive SOF/RBV, 21 discontinued treatment due to adverse event (n=9); loss to follow-up (n=4), withdrew consent (n=3), death (n=2), non-compliance with study drug (n=2) and lack of efficacy (n=1). By comparison the SOF/VEL arm has two discontinuations (lack of efficacy and non-adherence) out of a possible 278.[31] For all other criteria the ERG agrees with the CS's assessment.

For Astral 2 again an interactive web response system was used. Demographic and baseline clinical characteristics were generally well balanced. The study was open-label. There were similar proportions of discontinuations in both treatment arms. Modified ITT was used and the analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data.[25]

ERG comment: The ERG agrees with the CS's quality assessment of Astral 2.

Finally for Astral 1 demographic and baseline clinical characteristics were generally well balanced. The study was conducted in a double blind manor. Study drugs were dispended to patients in a blinded fashion as directed by the interactive web response system. In the event of a medical emergency where breaking the blinding was required to provide medical care to the patient, the investigator may have obtained treatment assignment for that patient. If a patient's treatment assignment was disclosed to the investigator, study treatment was discontinued for the patient. There were similar proportions of discontinuations in both treatment arms. Modified ITT was used and the analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data.

ERG comment: The ERG agrees with the CS's quality assessment of Astral 1.

4.1.5 Evidence synthesis

In section 4.9 of the CS (page 104) the company states "Not applicable"

ERG comment: The ERG agrees that a meta-analysis of SOF/VEL trials is not feasible. The three main SOF/VEL RCTs included in the submission were all in different populations (ASTRAL-3: GT3; ASTRAL-2: GT2; and ASTRAL-1: GT1, GT2, GT4, GT5, and GT6). In addition, the comparators were different in the three trials (ASTRAL-3: SOF/RBV 24 weeks; ASTRAL-2: SOF/RBV 12 weeks; and ASTRAL-1: placebo). Therefore, the results from these studies cannot be pooled.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

As explained in section 4.1.2 of this report, three comparative SOF/VEL trials have been included in the submission. Therefore, we will describe these three SOF/VEL RCTs (see Table 4.4) in terms of trial methodology (see Table 4.5) and baseline characteristics (see Table 4.6).

Table 4.4: Included comparative SOF/VEL trials

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
SOF/VEL RCTs						
1	Foster et al, 2015[31] Supporting information from CSR[40]	GS-US-342-1140 (ASTRAL-3)	Open label, Randomised, Multicentre (N=552)	CHC GT3 Treatment-naïve and treatment-experienced No cirrhosis and compensated cirrhosis	SOF/VEL for 12 weeks	SOF/RBV for 24 weeks
2	Foster et al, 2015[31] Supporting information from CSR[41]	GS-US-342-1139 (ASTRAL-2)	Open label, Randomised, Multicentre (N=269)	CHC GT2 Treatment-naïve and treatment-experienced No cirrhosis and compensated cirrhosis	SOF/VEL for 12 weeks	SOF/RBV for 12 weeks
3	Feld et al, 2015[32] Supporting information from CSR[21]	GS-US-342-1138 (ASTRAL-1)	Double blind, Randomised, Multicentre (N=706)	CHC GT1, GT2, GT4, GT5, GT6 Treatment-naïve and treatment-experienced No cirrhosis and compensated cirrhosis	SOF/VEL for 12 weeks	Placebo for 12 weeks

Source: CS, Table 11, page 64 and Table 12, page 65

Abbreviations: CHC, chronic hepatitis C; CSR, clinical study report; GT, genotype; RBV, ribavirin; RCT, randomised controlled trial; SOF, sofosbuvir; VEL, velpatasvir

Table 4.5: Summary of trial methodology for comparative SOF/VEL RCTs

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
Study objective	To compare the efficacy of treatment with SOF/VEL for 12 weeks with that of SOF/RBV for 24 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 for 12 weeks with that of SOF/RBV for 12 weeks as measured by the proportion of patients with SVR12 To evaluate the safety and tolerability of each treatment regimen	To evaluate the efficacy of treatment with SOF/VEL for 12 weeks in patients with CHC as measured by the proportion of patients with SVR12 To evaluate the safety and tolerability of treatment with SOF/VEL for 12 weeks
Location	76 sites in the United States, Canada, Europe (France, Germany, Italy, and the United Kingdom), Australia, and New Zealand. 11 sites (105 patients) in the United Kingdom.	51 sites in the United States.	81 sites in the United States, Canada, Europe (France, Germany, Belgium, Italy and the United Kingdom), and Hong Kong. 11 sites (104 patients) in the United Kingdom.
Design	Multicentre, randomised, open-label, active controlled, Phase III.		Multicentre, randomised, double-blind, placebo-controlled, Phase III.
Duration of study	Treatment duration: 12 or 24 weeks depending on treatment assignment. Follow-up: up to 24 weeks.	Treatment duration: 12 weeks. Follow-up: up to 24 weeks.	Treatment duration: 12 weeks. Follow-up: up to 24 weeks.
Eligibility criteria	GT3	GT2	GT1, GT2, GT4, GT5, GT6 or indeterminate
	HCV treatment-naïve or treatment-experienced. Cirrhosis permitted: Approximately 20%. Inclusion: 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. Exclusion: 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); prior exposure to SOF, NS5B or NS5A inhibitors; 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; clinically significant haemoglobinopathy. Contraindication to RBV (ASTRAL-2 and ASTRAL-3 only).		
Intervention(s) (n=) and	Patients were randomised in a 1:1 ratio to: SOF/VEL for 12 weeks (n=277)	Patients were randomised in a 1:1 ratio to: SOF/VEL for 12 weeks (n=135)	Patients infected with HCV GT1, GT2, GT4 or GT6:

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
comparator(s) (n=)	SOF/RBV for 24 weeks (n=275) Patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily, or 400 mg of SOF once daily plus RBV. RBV was administered orally twice daily, with the dose determined according to body weight (1,000 mg daily in patients with a body weight <75 kg, and 1,200 mg daily in patients with a body weight ≥75kg).	SOF/RBV for 12 weeks (n=134) Patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily, or 400 mg of SOF once daily plus RBV. RBV was administered orally twice daily, with the dose determined according to body weight (1,000 mg daily in patients with a body weight <75 kg, and 1,200 mg daily in patients with a body weight ≥75kg).	Randomised 5:1 to: SOF/VEL for 12 weeks (n=590) Placebo for 12 weeks (n=116) Patients in the placebo group were eligible for deferred treatment with SOF/VEL for 12 weeks. Patients infected with HCV GT5: Given the low prevalence of HCV GT5 infection, enrolment of only 20 patients was targeted for this group and 35 were eventually enrolled. These patients did not undergo randomisation and were pre-specified to receive SOF/VEL for 12 weeks. Patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily, or a placebo tablet to match the active treatment once daily.
Permitted and disallowed concomitant medications	Concomitant medications taken within 30 days of screening, up to and including 30 days after the last dose of study drug, were recorded. The following were prohibited from 28 days prior to the baseline/Day 1 visit through the EOT visit: Haematologic stimulating agents (e.g. ESAs, GCSF, TPO mimetics) Chronic systemic immunosuppressants including: Corticosteroids (prednisone equivalent of >10 mg/day for >2 weeks); Azathioprine; and Monoclonal antibodies (e.g. infliximab) Investigational agents or devices for any indication Drugs disallowed according to prescribing information of SOF or RBV (ASTRAL-2 and ASTRAL-3 only) Concomitant use of medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e. P-glycoprotein) which may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug(s) or these medications. Examples of representative medications that were prohibited from 21 days prior to baseline/Day 1 through EOT are listed in the clinical study protocol. Medications for disease conditions excluded from the protocol (e.g., HIV-1, active cancer, transplantation) were not listed as concomitant medications and were disallowed in the study.		
Primary outcomes	SVR12, defined as HCV RNA <LLOQ, 12 weeks after the end of treatment, in the FAS population. The LLOQ was 15 IU/mL.		

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
Secondary outcomes (including scoring methods and timings of assessments)	Proportion of patients with SVR (HCV RNA<LLOQ) at 4 weeks and 24 weeks after end of treatment (SVR4 and SVR24) The proportion of patients with HCV RNA<LLOQ on treatment by study visit HCV RNA change 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 Characterisation of drug resistance at baseline, during and after therapy: Deep sequencing of the HCV NS5A and NS5B coding regions was performed on samples obtained from all patients at baseline and again for all patients with virologic failure. Sequences that were obtained at the time of virologic failure were compared with sequences from baseline samples to detect resistance-associated variants that emerged during treatment. Resistance-associated variants that were present in >1% of sequence reads were reported. ALT normalisation HRQoL (SF-36, CLDQ-HCV, FACIT-F and WPAI)		

Source: CS, Table 12, page 65 and Table 13, page 70

Abbreviations: AE, adverse event; CHC, chronic hepatitis C; CLDQ, Chronic Liver Disease Questionnaire; CPT, Child-Pugh-Turcotte; CV, cardiovascular; ECG, electrocardiogram; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; FACIT-F, Fatigue Index; FAS, full analysis set; GCSF, granulocyte colony stimulating factor; GI, gastrointestinal; GT, genotype; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, Health Related Quality of Life; IFN interferon; INR, International Normalised Ratio; IWRS, interactive web response system; LLOQ, lower limit of quantitation; MELD, Model for End-Stage Liver Disease; RBV, ribavirin; RNA, ribonucleic acid; SF-36, 36-Item Short-Form Survey; SOF, sofosbuvir; SVR, sustained virologic response; TPO, thrombopoietin; VEL, velpatasvir; WPAI, Work Productivity and Activity Impairment

Table 4.6: Baseline characteristics for comparative SOF/VEL RCTs

	ASTRAL-3 (FAS)		ASTRAL-2 (FAS)		ASTRAL-1 (FAS)	
Characteristic	SOF/VEL N=277	SOF/RBV N=275	SOF/VEL N=134	SOF/RBV N=132	SOF/VEL N=624	Placebo N=116
Mean age (range), years	49 (21–76)	50 (19–74)	57 (26–81)	57 (23–76)	54 (18–82)	53 (25–74)
Male, n (%)	170 (61)	174 (63)	86 (64)	72 (55)	374 (60)	68 (59)
Mean BMI (range), kg/m2[†]	26 (17–48)	27 (17–56)	28 (17–45)	29 (19–61)	27 (17–57)	26 (18–40)
Race, n (%)[‡]						
White	250 (90)	239 (87)	124 (93)	111 (84)	493 (79)	90 (78)
Black	3 (1)	1 (<1)	6 (4)	12 (9)	52 (8)	11 (9)
Asian	23 (8)	29 (11)	1 (1)	5 (4)	62 (10)	11 (9)
Other	1 (<1)	6 (2)	3 (2)	4 (3)	14 (2)	4 (3)
HCV genotype, n (%)						
1a					210 (34)	46 (40)
1b					118 (19)	19 (16)
2			134 (100)	132 (100)	104 (17)	21 (18)
3	277 (100)	275 (100)				
4					116 (19)	22 (19)
5[§]					35 (6)	0
6					41 (7)	8 (7)
Mean HCV RNA±SD, log10 IU/mL	6.2±0.72	6.3±0.71	6.5±0.78	6.4±0.74	6.3±0.66	6.3±0.58
HCV RNA≥800,000 IU/mL, n (%)	191 (69)	194 (71)	111 (83)	101 (77)	461 (74)	87 (75)
IL28B genotype, n (%)						
CC	105 (38)	111 (40)	55 (41)	46 (35)	186 (30)	36 (31)
CT	148 (53)	133 (48)	61 (46)	64 (48)	339 (54)	53 (46)
TT	24 (9)	31 (11)	18 (13)	22 (17)	94 (15)	26 (22)

	ASTRAL-3 (FAS)		**ASTRAL-2 (FAS)**		**ASTRAL-1 (FAS)**	
Characteristic	SOF/VEL N=277	SOF/RBV N=275	SOF/VEL N=134	SOF/RBV N=132	SOF/VEL N=624	Placebo N=116
Missing data					5 (1)	1 (1)
Compensated cirrhosis, n (%)	80 (29)	83 (30)	19 (14)	19 (14)	121 (19)	21 (18)
Previous HCV treatment, n (%)						
No	206 (74)	204 (74)	115 (86)	112 (85)	423/624 (68)	83/116 (72)
Yes	71 (26)	71 (26)	19 (14)	20 (15)	201/624 (32)	33/116 (28)
Type of previous HCV treatment, n/total (%)						
DAA/PR	[redacted]	[redacted]	[redacted]	[redacted]	56/201 (28)	6/33 (18)
PR	[redacted]	[redacted]	[redacted]	[redacted]	122/201 (61)	24/33 (73)
Non P or PR					23/201 (11)	3/33 (9)
Other	[redacted]	[redacted]	[redacted]	[redacted]		
Response to previous HCV treatment, n/total (%)						
No response	20/71 (28)	24/71 (34)	3/19 (16)	3/20 (15)	[redacted] (48)	[redacted]
Relapse/breakthrough	51/71 (72)	47/71 (66)	16/19 (84)	17/20 (85)	[redacted] (51)	[redacted]

Source: CS, Table 20, page 81; Table 21, page 83; and Table 22, page 84

Abbreviations: BMI, body mass index; DAA, direct acting antiviral; FAS, Full analysis set; HCV, hepatitis C virus; Peg-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; VEL, velpatasvir

† BMI is the weight in kg divided by the height squared in metres; ‡ race was self-reported; § Patients with HCV GT5 infection did not undergo randomisation but were enrolled in the SOF/VEL group.

The CS reports clinical effectiveness results according to the primary objective (SVR12) for each of the included SOF/VEL RCTs (n=3). Here we will only report results for the RCTs that include a relevant comparator: ASTRAL-3, comparing SOF/VEL for 12 weeks with SOF/RBV for 24 weeks, and ASTRAL-2, comparing SOF/VEL for 12 weeks with SOF/RBV for 12 weeks. The remaining trial compared SOF/VEL with placebo (resulting in 0% SVR12). Results of the placebo controlled randomised trial in terms of adverse events will be reported below.

4.2.1 Results

ASTRAL-3

Among patients with GT3 HCV infection the SVR rate 12 weeks after treatment with SOF/VEL for 12 weeks was 95.3% [redacted] compared with 80.7% [redacted] in patients who received 24 weeks of treatment with SOF/RBV.

The primary efficacy endpoint was met. The SVR12 rate for the SOF/VEL 12 week group was statistically non-inferior to the SVR12 rate for the SOF/RBV 24 week group; strata-adjusted difference [redacted] with the lower bound of the two-sided 95% CI for the difference being greater than the pre-specified non-inferiority margin of −10%.

SOF/VEL 12 weeks was also shown to be superior to SOF/RBV for 24 weeks (p<0.001; Cochran-Mantel-Haenszel [CMH] test stratified by cirrhosis status and prior treatment experience).

Overall, results from the HRQoL questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) indicated that no on-treatment decrements in HRQoL were observed in the SOF/VEL 12 week group. In the SOF/RBV 24 week group, statistically significant (p<0.05) worsening in HRQoL was observed between baseline and end-of-treatment for the SF-36 (domains of role physical, social functioning, mental health, and mental component) and WPAI: Hep C (percent overall work impairment due to HCV).

ASTRAL-2

Among patients with GT2 HCV infection the SVR rate 12 weeks after treatment with SOF/VEL for 12 weeks was 99.3% [redacted] compared with [redacted] in patients who received 12 weeks of treatment with SOF/RBV.

The primary efficacy endpoint was met. The SVR12 rate for the SOF/VEL 12 week group was statistically non-inferior to the SVR12 rate for the SOF/RBV 12 week group; strata-adjusted difference 5.2% (95% CI: 0.2, 10.3) with the lower bound of the two-sided 95% CI for the difference being greater than the pre-specified non-inferiority margin of −10%.

SOF/VEL 12 weeks was also shown to be superior to SOF/RBV for 12 weeks (p=0.018; CMH test stratified by cirrhosis status and prior treatment experience).

Overall, results from all HRQoL questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) indicated that no on-treatment decrements in HRQoL were observed in the SOF/VEL 12 week group. In the SOF/RBV 12 week group, statistically significant (p<0.05) worsening in HRQoL was observed between baseline and end-of-treatment for the SF-36 domain of role emotional and a statistically significant improvement was observed for bodily pain.

4.2.2 Adverse events

ASTRAL-3

In ASTRAL-3, a lower percentage of patients in the SOF/VEL 12 week group experienced any AE (n=245; 88%) compared with SOF/RBV for 24 weeks (n=260; 95%), predominately due to a higher percentage of AEs known to be associated with RBV: fatigue (26% vs 38%), insomnia (11% vs 27%), nausea (17% vs 21%), irritability (8% vs 15%), cough (5% vs 13%), pruritus (3% vs 13%), and dyspepsia (3% vs 11%) (See Table 4.7).

Table 4.7: ASTRAL-3 adverse events summary

Adverse events, n (%)	SOF/VEL 12 week (N=277)	SOF/RBV 24 week (N=275)	Relative risk (95% CI)
≥1 AE	245 (88.4)	260 (94.5)	0.94 (0.89, 0.98)
≥1 treatment-related AE	[redacted]	[redacted]	0.78 (0.70, 0.88)
Grade 3 or 4 AE	[redacted]	[redacted]	0.52 (0.26, 1.02)
Grade 3 AE	[redacted]	[redacted]	0.60 (0.30, 1.19)
Grade 4 AE	[redacted]	[redacted]	0.14 (0.01, 2.73)
Grade 3/4 AEs in >1 patient			
Headache	[redacted]	[redacted]	0.20 (0.01, 4.12)
Abdominal pain	[redacted]	[redacted]	0.20 (0.01, 4.12)
Anxiety	[redacted]	[redacted]	0.20 (0.01, 4.12)
≥1 SAE	6 (2.2)	15 (5.5)	0.40 (0.16, 1.01)
≥1 treatment-related SAE	[redacted]	[redacted]	0.33 (0.01, 8.09)
Deaths	0	3 (1.1)	0.14 (0.01, 2.73)
Discontinuation due to AEs	0	9 (3.3)	0.05 (0.00, 0.89)
Common AEs[†]			
Headache	90 (32.5)	89 (32.4)	1.00 (0.79, 1.28)
Fatigue	71 (25.6)	105 (38.2)	0.67 (0.52, 0.86)
Insomnia	31 (11.2)	74 (26.9)	0.42 (0.28, 0.61)
Nausea	46 (16.6)	58 (21.1)	0.79 (0.56, 1.12)
Nasopharyngitis	34 (12.3)	33 (12.0)	1.02 (0.65, 1.60)
Irritability	23 (8.3)	40 (14.5)	0.57 (0.35, 0.93)
Cough	14 (5.1)	35 (12.7)	0.40 (0.22, 0.72)
Pruritus	8 (2.9)	35 (12.7)	0.23 (0.11, 0.48)
Dyspepsia	9 (3.2)	30 (10.9)	0.30 (0.14, 0.62)
Back pain	[redacted]	[redacted]	1.24 (0.71, 2.18)
Asthenia	[redacted]	[redacted]	0.61 (0.34, 1.11)
Diarrhoea	[redacted]	[redacted]	0.95 (0.52, 1.70)
Dizziness	[redacted]	[redacted]	0.71 (0.37, 1.35)
Constipation	[redacted]	[redacted]	0.61 (0.31, 1.20)
Arthralgia	[redacted]	[redacted]	0.45 (0.22, 0.94)
Dyspnoea	[redacted]	[redacted]	0.36 (0.16, 0.80)

Adverse events, n (%)	SOF/VEL 12 week (N=277)	SOF/RBV 24 week (N=275)	Relative risk (95% CI)
Abdominal pain	[redacted]	[redacted]	0.52 (0.25, 1.10)
Muscle spasms	[redacted]	[redacted]	0.81 (0.40, 1.64)
Rash	[redacted]	[redacted]	1.06 (0.52, 2.16)
Anxiety	[redacted]	[redacted]	0.33 (0.14, 0.77)
Vomiting	[redacted]	[redacted]	0.40 (0.18, 0.89)
Dry skin	[redacted]	[redacted]	0.08 (0.02, 0.33)
Anaemia	[redacted]	[redacted]	0.04 (0.01, 0.30)
Myalgia	[redacted]	[redacted]	0.66 (0.30, 1.45)
Sleep disorder	[redacted]	[redacted]	0.60 (0.27, 1.34)
Dyspnoea exertional	[redacted]	[redacted]	0.15 (0.04, 0.50)
Decreased appetite	[redacted]	[redacted]	0.57 (0.24, 1.33)
Disturbance in attention	[redacted]	[redacted]	0.50 (0.20, 1.21)
Pyrexia	[redacted]	[redacted]	0.28 (0.09, 0.85)

Source: CS, Table 53, page 173.
Abbreviations: AE, adverse event; CI, confidence interval; SAE, serious adverse event.
†Common AEs were those that occurred in ≥5% of patients in any treatment group.

ASTRAL-2

In ASTRAL-2, a smaller percentage of patients in the SOF/VEL 12 week group experienced any AE compared with the SOF/RBV 12 week group (69% vs 77%, respectively). This was largely due to higher rates of AEs typically associated with RBV such as fatigue (15% vs 36%), headache (18% vs 22%), nausea (10% vs 14%) and insomnia (4% vs 14%) (See Table 4.8).

Table 4.8: ASTRAL-2 adverse events summary

Adverse events, n (%)	SOF/VEL 12 week (N=134)	SOF/RBV 12 week (N=132)	Relative risk (95% CI)
≥1 AE	92 (68.7)	101 (76.5)	0.90 (0.77, 1.04)
≥1 treatment-related AE	[redacted]	[redacted]	0.59 (0.45, 0.78)
Grade 3 or 4 AE	[redacted]	[redacted]	0.99 (0.20, 4.79)
Grade 3 AE	[redacted]	[redacted]	0.99 (0.20, 4.79)
Grade 4 AE	[redacted]	[redacted]	-
Grade 3/4 AEs in >1 patient			
Anxiety	[redacted]	[redacted]	4.93 (0.24, 101.64)
≥1 SAE	2 (1.5)	2 (1.5)	0.99 (0.14, 6.89)
≥1 treatment-related SAE	[redacted]	[redacted]	-
Deaths	2 (1.5)	0	4.93 (0.24, 101.64)
Discontinuation due to AEs	1 (0.7)	0	2.96 (0.12, 71.91)
Common AEs†			
Fatigue	20 (14.9)	47 (35.6)	0.42 (0.26, 0.67)
Headache	24 (17.9)	29 (22.0)	0.82 (0.50, 1.32)
Nausea	14 (10.4)	19 (14.4)	0.73 (0.38, 1.39)

Adverse events, n (%)	SOF/VEL 12 week (N=134)	SOF/RBV 12 week (N=132)	Relative risk (95% CI)
Insomnia	6 (4.5)	18 (13.6)	0.33 (0.13, 0.80)
Anxiety	[redacted]	[redacted]	0.99 (0.38, 2.55)
Arthralgia	[redacted]	[redacted]	0.74 (0.26, 2.07)
Irritability	4 (3.0)	9 (6.8)	0.44 (0.14, 1.39)
Pruritus	6 (4.5)	7 (5.3)	0.84 (0.29, 2.45)
Upper respiratory tract infection	[redacted]	[redacted]	1.58 (0.53, 4.69)
Vomiting	[redacted]	[redacted]	0.62 (0.21, 1.83)
Abdominal pain	[redacted]	[redacted]	0.70 (0.23, 2.16)
Sinusitis	[redacted]	[redacted]	1.38 (0.45, 4.24)
Dizziness	[redacted]	[redacted]	0.37 (0.10, 1.36)
Nasopharyngitis	8 (6.0)	2 (1.5)	3.94 (0.85, 18.21)
Back pain	[redacted]	[redacted]	0.28 (0.06, 1.33)
Rash	[redacted]	[redacted]	0.28 (0.06, 1.33)
Anaemia	[redacted]	[redacted]	0.06 (0.00, 0.99)

Source: CS, Table 54, page 176.
Abbreviations: AE, adverse event; CI, confidence interval; SAE, serious adverse event.
†Common AEs were those that occurred in ≥5% of patients in any treatment group.

ASTRAL-1

Overall, SOF/VEL for 12 weeks was well tolerated with patients experiencing similar type, incidence, and severity of AEs as patients in the placebo 12 week group.

Incidence rates in the SOF/VEL and placebo groups of any AE (485 [78%] vs 89 [77%] patients, respectively), and of the most common individual AEs, were generally comparable (See Table 4.9). The most common AEs were headache, fatigue, nausea and nasopharyngitis.

Table 4.9: ASTRAL-1 adverse events summary

Adverse events, n (%)	SOF/VEL 12 week (N=624)	Placebo (N=116)	Relative risk (95% CI)
≥1 AE	485 (77.7)	89 (76.7)	1.01 (0.91, 1.13)
≥1 treatment-related AE	[redacted]	[redacted]	1.09 (0.88, 1.35)
Grade 3 or 4 AE	[redacted]	[redacted]	3.35 (0.45, 24.82)
Grade 3 AE	[redacted]	[redacted]	2.97 (0.40, 22.21)
Grade 4 AE	[redacted]	[redacted]	0.94 (0.05, 19.37)
Grade 3/4 AEs in >1 patient			
Headache	[redacted]	[redacted]	1.31 (0.07, 25.20)
≥1 SAE	15 (2.4)	0	5.80 (0.35, 96.32)
≥1 treatment-related SAE	[redacted]	[redacted]	-
Deaths	1 (0.2)	0	0.56 (0.02, 13.70)
Discontinuation due to AEs	1 (0.2)	2 (1.7)	0.09 (0.01, 1.02)
Common AEs†			

Adverse events, n (%)	SOF/VEL 12 week (N=624)	Placebo (N=116)	Relative risk (95% CI)
Headache	182 (29.2)	33 (28.4)	1.03 (0.75, 1.40)
Fatigue	126 (20.2)	23 (19.8)	1.02 (0.68, 1.52)
Nasopharyngitis	79 (12.7)	12 (10.3)	1.22 (0.69, 2.17)
Nausea	75 (12.0)	13 (11.2)	1.07 (0.62, 1.87)
Insomnia	50 (8.0)	11 (9.5)	0.84 (0.45, 1.57)
Diarrhoea	48 (7.7)	8 (6.9)	1.12 (0.54, 2.30)
Asthenia	41 (6.6)	9 (7.8)	0.85 (0.42, 1.69)
Arthralgia	40 (6.4)	9 (7.8)	0.83 (0.41, 1.66)
Cough	39 (6.3)	4 (3.4)	1.81 (0.66, 4.98)
Back pain	29 (4.6)	11 (9.5)	0.49 (0.25, 0.95)
Myalgia	25 (4.0)	6 (5.2)	0.77 (0.32, 1.85)

Source: CS, Table 55, page 177.
Abbreviations: AE, adverse event; CI, confidence interval; SAE, serious adverse event.
†Common AEs were those that occurred in ≥5% of patients in any treatment group.

ERG comment: These three trials provide clear evidence for the effectiveness of SOF/VEL and its adverse events in different populations and versus different comparators. However, the trials include only one relevant comparator: SOF/RBV. Therefore, these trials provide very little evidence for the decision problem at hand: The relative effectiveness of SOF/VEL versus the comparators mentioned in the NICE scope.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As described in section 4.1.2 of this report, 89 publications and 10 conference abstracts (reporting on 100 studies) were identified as meeting the eligibility criteria.

Sixty publications and 10 conference abstracts (total of 70 publications/abstracts covering 71 studies) reported on randomised comparisons between the interventions listed in Table 9 of the CS (Eligibility criteria), including SOF/VEL and comparators identified in the NICE scope for this appraisal, and were used to assess the feasibility of performing an NMA. These 71 studies are listed in Table 31 of the CS.

The CS states that only evidence networks for GT1 treatment-naïve and GT3 treatment-naïve patients could be constructed and analysed in the NMA, because of a lack of data for the other populations. For patient populations where an NMA was feasible (GT1 treatment-naïve and GT3 treatment-naïve), these analyses had several limitations: the NMA does not provide relative treatment effects by treatment history, sub genotype and fibrosis stage. As such, the results from the NMA could not be considered appropriate for the economic model, which required analyses comparing SOF/VEL to the comparators listed in the NICE scope stratified by treatment history and cirrhosis status. The exception was for GT2 treatment-naïve patients (non-cirrhotic and cirrhotic) where it was possible to compare SOF/VEL with PR using a Bucher indirect comparison with the results from the FISSION and ASTRAL-2 trials.

The results of the NMA were not considered to be robust or credible for use in the economic model. The inputs were therefore based on results from individual trials which provided relevant results,

stratified by treatment history and cirrhosis status, an approach which was felt by the company to be more transparent and justifiable and in line with the requirements of the NICE scope.

ERG comment: Full details of the statistical methods used for the two NMAs which were possible, were reported in the submission. These were clearly reported and appear to be appropriate. However, the decision was made not to use their results in the economic model. Justification for this was provided in section 4.10.8 on pages 126 to 127 and clinical expert opinion was also sought. The ERG agrees that, given that the economic model requires separate results for cirrhotic and non-cirrhotic patients, the NMA results were not suitable for use in the economic analysis. Further discussion about the choice of individual study results for use in the model is provided in section 4.4 below.

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

As described in the previous section, NMA results were not used for the economic model. Instead results from what the company describes as a 'naive comparison' (CS, section 4.10.9, page 130) were used in the economic model. However, the term 'naive comparison' is slightly misleading as no comparisons were made. The company simply selected one SVR rate from individual arms from included studies. The justification for each choice for a specific intervention and population is provided in Table 39 of the CS.

The critique of the ERG is based on three points:

1. The company selected one source for each intervention and population. Choices were often arbitrary and selecting results from a single arm of a study means that results are open to all the risks of bias associated with observational studies.
2. SVR rates are selected from a pool of RCTs retrieved through the company's original search. However, other study designs should have been included in the searches (uncontrolled studies, case series, etc.) because data are taken from individual study arms.
3. Sometimes multiple SVR rates are presented within a study; the choice for one particular SVR rate within a study is arbitrary again.

Point1: For each intervention and population, the CS specifies in Table 39 which study was used as the source for SVR data in the economic model. Using only one source for each intervention and population increases the chance of bias and cherry-picking. Alternatively, the company could have listed the available options and calculated a mean.

In the clarification letter the ERG requested such an analysis (Question B2a), but the company declined to perform such an analysis. Instead, the company provided additional justifications for those treatments with more than one possible source of SVR rate in specific patient subgroups. For instance for SOF/RBV (24w) in patients with GT3 TN (NC and CC) the ASTRAL-3 trial was chosen as the source of SVR rate. Alternative sources were the BOSON and VALENCE trials.

For BOSON the company provides an analysis showing that the cost effectiveness results remain unchanged regardless of whether ASTRAL-3 or BOSON is used to provide an SVR rate for SOF/RBV (24w). However, this is only one case where an alternative source could have been used. In total for four out of six interventions in patients with GT3 TN (NC and CC) alternative sources could have been used. It is very well possible that using alternative sources in all four instances will change the cost effectiveness results.

For VALENCE, the company stated that this trial "was initially designed to compare SOF/RBV (12 weeks) with placebo in patients with HCV GT2 or GT3 infection. However, emerging data from the Phase III FUSION trial indicated that patients with HCV GT3 infection had higher response rates when treated for 16 weeks compared with 12 weeks. As a result the VALENCE trial was unblinded, and treatment for all patients with HCV GT3 infection was extended to 24 weeks and the placebo group terminated. The trial was redefined as a descriptive study to characterise SVR rates in patients with HCV GT2 infection treated for 12 weeks, and in patients with HCV GT3 infection treated for 24 weeks, with no plans for hypothesis testing. For this reason, the VALENCE trial did not fulfil the criteria for inclusion in the systematic literature review described in section 4.1 of the company submission and was considered unsuitable for use as a source of SVR rate in the economic model."[1] However, given that estimates were taken from single arms of studies, this is not a valid reason to exclude this study.

Overall, the justifications provided by the company for each selected SVR rate seem valid. However, it would be quite easy to provide an equally valid justification for most of the alternative sources. Therefore, the main problem with this method of selecting inputs for the economic model still stands: using only one source for each intervention and population increases the chance of bias and cherry-picking.

Point 2: The selected studies for each SVR rate have been chosen from a pool of studies retrieved through the company's search strategy. However, the inclusion criteria for this pool of studies specified that each study should be a randomised controlled trial (see inclusion criteria: CS, Table 9, page 61). Now that single arms are used from each study, it no longer matters whether studies are randomised or even whether they include control arms. Therefore, all types of study design are valid for inclusion, including cohort studies and case series. This means that studies from outside the pool of studies should have been included and assessed for inclusion in the naive comparison. In addition, sometimes sources are from studies outside of the pool (taken from previous STAs); it is unclear how these were found.

Point 3: Once a specific study has been selected, it is still difficult to decide which SVR rate to choose for a specific population. For instance, in the economic model, the company has selected 94% as the SVR rate for LDV/SOF for treatment naive people with GT1a without cirrhosis and for treatment naive people with GT1b without cirrhosis based on the study by Kowdley et al., 2014[44]. Kowdley et al., 2014 includes previously untreated patients with HCV genotype 1 infection without cirrhosis to receive LDV/SOF for eight weeks or 12 weeks. SVR rates were 94% for eight weeks and 95% for 12 weeks. More specifically, for patients with GT1a, SVR rates were 93% for eight weeks and 95% for 12 weeks; and for patients with GT1b, SVR rates were 98% for eight weeks and 98% for 12 weeks. This means that, instead of using one SVR rate (94%) for GT1a and GT1b, the company could have chosen different SVR rates for GT1a and GT1b: 94% for GT1a and 98% for GT1b. Therefore, the choice of SVR rate from each study is arbitrary and again increases the chance of bias and cherry-picking.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The conclusion from the SOF/VEL trials is that SOF/VEL has high SVR rates in all genotypes. In addition, SOF/VEL has a relative favourable safety and tolerability profile. Generally, the three SOF/VEL trials were well conducted. However, ASTRAL-3 and 2 were open-label studies; therefore,

care providers, participants and outcome assessors were not blinded to treatment allocation. In addition, in ASTRAL-3 there was a greater number of dropouts in the SOF/RBV treatment arm than in the intervention arm (n=21, vs. n=2 in SOF/VEL arm). Both issues mean that these trials are at a higher risk of bias.

The main concern regarding clinical effectiveness is that comparator data (for SVR12 and AEs) were taken from single arms of randomised controlled trials (RCTs). Overall, the justifications provided by the company for each selected SVR rate seem valid. However, it would be quite easy to provide an equally valid justification for most of the alternative sources. Therefore, the main problem with this method of selecting inputs for the economic model still stands: using only one source for each intervention and population increases the chance of bias and cherry-picking.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Objective of cost effectiveness review

A literature review was conducted to identify all published studies that assessed the cost effectiveness of DAAs for treating chronic hepatitis C. Searches were reported for MEDLINE and MEDLINE In-Process, Embase, the Health Technology Assessment Database (HTA), the NHS Economic Evaluation Database (NHS EED) and EconLit. The host provider for each database was listed and the date the searching was conducted was provided. Database date spans were provided in the clarification response.[28] No date or language limits were applied. The ERG noted that extensive electronic searches of online and PDF conference abstract were carried out, from 2014-2016 (where available). These searches covered five different conference proceedings, including: European Association for the Study of the Liver (EASLD, 2015), American Association for the Study of Liver Diseases (AASLD, 2014-2015), Viral Hepatitis Congress (VHC, 2014-2015), International Society for Pharmacoeconomics and Outcomes Research (ISPOR, 2014-2015), and Asian Pacific Association for the Study of the Liver (APASL, 2014-2016). Search strategies for the database searches were provided in the Appendix 12 of the CS[25] and were well reported and reproducible.

ERG comment: The search meets the requirements detailed in the NICE guide to the methods of technology appraisal.[24] For the most part, the database searches were clearly structured and used combinations of index terms appropriate to the resource searched, free text and a number of synonyms for the condition, intervention and most of the comparators. The ERG considered the concurrent Medline and Embase searches to be satisfactory. It is not clear whether a validated study design filter was used for the cost effectiveness facet of search terms.

The ERG considered the search of the Health Technology Assessment (HTA) and NHS Economic Evaluation Database (NHS EED) to be overly restrictive, as the search strategy used contained a study design filter limiting the results to economic evaluations and QALYS/ICERs. The ERG considered this to be overly restrictive and unnecessary as the Cochrane databases are pre-filtered resources, i.e. the database of relevance to this search, NHS EED, only contains economic evaluations. The ERG re-ran the CS HTA/NHS EED search to assess how many records were missed by applying this study design limit. An additional 52 records from the HTA database were retrieved by the ERG approach which is presented in section 5.1. The ERG screened the additional records and none of the missed records were classified as relevant.

5.1.2 Inclusion/exclusion criteria used in the study selection

The eligibility criteria for study selection are presented in Table 5.1. These were used during title and abstract screening and subsequently for full text review.

Table 5.1: Eligibility criteria used in search strategy (CS Appendix 12 Table 14)

	Inclusion criteria	Exclusion criteria
Population	Adult patients (aged ≥18 years) with chronic HCV infection of any genotype Populations where all patients had HIV or HBV co-infection were permitted	Populations where the majority of patients were aged <18 years, patients without HCV infection, patients with acute phase HCV infection (less than 6 months since infection), populations defined by a specific comorbidity (other than HIV or HBV)[a]
Interventions	Regimens including sofosbuvir or other DAAs that have not been discontinued (including boceprevir, daclatasvir, danoprevir, dasabuvir, elbasvir, grazoprevir, ledipasvir, ombitasvir, simeprevir, telaprevir, and velpatasvir)	Studies comparing two or more failed or obsolete therapies, such as regimens that do not contain any DAAs (e.g. interferon therapies) Studies investigating screening, prevention, treatment strategies (e.g. immediate vs delayed treatment) or any non-pharmacological interventions
Comparators	Regimens including sofosbuvir or current DAAs as above, regimens that do not contain any DAAs (e.g. interferon therapies), or no treatment/best supportive care	
Outcomes	The outcomes of relevant study designs, including: • Costs • Life years • QALYs • Incremental costs and QALYs • ICERs	Studies presenting irrelevant outcomes only. Studies presenting only costs or resource use without relative consideration of health effects. Studies that did not present relevant outcomes specifically for the population of interest.
Study design	Comparative economic evaluations, including HTAs presenting original economic evaluations Cost-effectiveness analyses Cost-utility analyses Cost-benefit analyses Cost-consequence analyses Cost-minimisation analyses	Non-systematic reviews, editorials, case reports, conference abstracts older than two years (i.e. March 2014 or earlier)
	Systematic reviews, meta-analyses and HTAs were included at title/abstract review and used to hand-search additional potentially relevant articles. They were then excluded at full text review, with the exception of HTAs presenting original economic evaluations, which were included.	
Language restrictions	English language	Any other language

a Incidental comorbidities, e.g. studies where a percentage of patients have a particular comorbidity, were included. Studies to be excluded were those where all patients had a comorbidity not of interest to this review, and this was an inclusion criterion of the study. Liver fibrosis, cirrhosis and hepatocellular carcinoma are part of the HCV disease process and were not considered as comorbidities

ERG comment: The ERG considers the eligibility criteria suitable for the objective of the company literature review.

5.1.3 Included/excluded studies in the cost effectiveness review

The databases search identified 621 records. Of those, 579 were selected for abstract review after removal of duplicates and 248 were included for full text review after title and abstract screening. Finally, 143 studies were included from the databases search. In addition, seven HTA submissions and two congress abstracts were retrieved from the hand search. These were also included in the review which results in a total of 152 relevant studies included.

Twenty-five economic evaluations were performed in the UK and six were considered of particular interest. Data were extracted from these six assessments.[16-18, 45-47] Appendix 12 provides an overview of the 25 studies and the reasons for (not) extracting data from these studies. The data extraction is also presented in Appendix 12.[25]

ERG comment: The ERG considered that several studies containing evaluations of comparators present in the scope were not extracted (clarification question C1)[48] and requested the company to extract data from an additional seven studies.[11-14, 49-51] The company partially met this request by extracting data from two[14, 51] out of these seven studies (response to clarification question C1).[28]

5.1.4 Conclusions of the cost effectiveness review

The company provided an overview of these six studies but no conclusion has been formulated in the CS.

ERG comment: No comment, as no conclusion was formulated by the company.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.2: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source / Justification	Signpost (location in CS)
Model	A Markov state-transition model was adapted from the model by Dusheiko and Roberts, 1995.[52] The same model structure is used for all patients irrespective of HCV genotype or treatment experience.	This model structure represents the natural history of CHC and has been widely used and adapted for HTA purposes.	Section 5.2.2.1 and 5.2.2.2
States and events	The following health states are incorporated in the model: • Non-cirrhotic • Compensated cirrhosis • Non-cirrhotic with SVR • Compensated cirrhosis with SVR • Decompensated cirrhosis • Decompensated cirrhosis with SVR • Hepatocellular carcinoma • Liver transplant • Post-liver transplant • Death	The health states earlier in disease progression than compensated cirrhosis are represented as a single health state (non-cirrhotic), rather than being separated 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. Moreover, this structure offers the best fit for the Gilead pivotal Phase III trials for SOF/VEL, in which patients were split between non-cirrhotic and cirrhotic defined as per the Fibrotest and Fibroscan scores.	Sections 5.2.2.1-5.2.2.3
Comparators	• 3D (12 w) • DCV/SOF (12w) • LDV/SOF (8/12w) • 2D/RBV (12/24w) • 3D/RBV (12/24w) • DCV/PR (48w) • DCV/SOF/RBV (12/24w)	The comparators DCV/SOF/RBV (12/24w) in GT3 cirrhotic patients, DCV/PR (48w) in GT4 patients, SMV/PR in GT4 patients and 2D 24w in GT4 for cirrhotic patients are listed in the scope, but are only included in scenario analyses. This is because the company considered	Section 5.2.3 and response to clarification question C

	Approach	Source / Justification	Signpost (location in CS)
	• LDV/SOF/RBV (12w) • PR (24/48w) • SMV/PR • SOF/PR (12w) • SOF/RBV (12/24w) • BSC	them to be irrelevant to clinical practice in the UK and/or to be always dominated.	
Population	People with chronic HCV. This population is subdivided by HCV genotype, previous treatment (treatment-naïve and treatment- experienced), cirrhosis state, and IFN eligibility.		Section 5.2.1
Treatment effectiveness	Incorporated using SVR rates		Section 4.10
Adverse events	Costs related to adverse events were considered.		Sections 5.5.4 and 5.6.1
Health related QoL	Health state utility values were obtained from Wright et al., 2006[53] and Ratcliffe et al., 2002[54] A utility increment, obtained from Vera-Llonch et al., 2013[55], is applied to patients who have achieved a SVR and utility increments and decrements are applied to health state utility values when patients are receiving treatment. These are based on different trials investigating treatments for CHC.[44, 56-59]	Utility values were elicited during the ASTRAL trials[31-33] through the SF-36 but were not used in the cost effectiveness model due to the unavailability of these data at the time of submission.	Section 5.2.7
Resource utilisation and costs	The following cost categories were considered • Drug costs • Monitoring costs • Health state costs • Adverse event costs		Section 5.5.2
Discount rates	Discount of 3.5% for utilities and costs	As per NICE scope	Section 5.2.2.4
Sub groups	Subgroups are defined based on HCV genotype, previous treatment, cirrhosis state and IFN eligibility.		Section 5.2.1

	Approach	Source / Justification	Signpost (location in CS)
Sensitivity analysis	Both DSA and PSA are performed		Section 5.8

ADP = adenosine diphosphate; ASA = acetylsalicylic acid; BID = twice daily; CS = company submission; CV = cardiovascular; DSA = deterministic sensitivity analysis; EQ-5D = European Quality of Life-5 Dimensions; ICER = incremental cost effectiveness ratio; mg = milligram; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted Life Year; TIMI = Thrombolysis in Myocardial Infarction

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: NICE reference case checklist

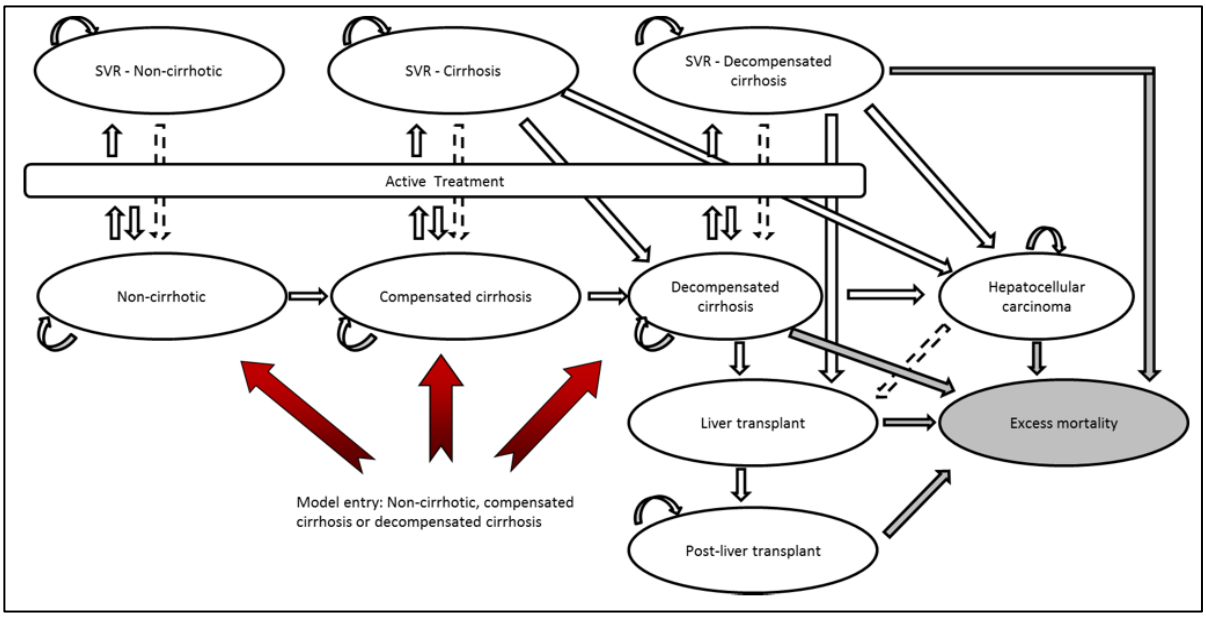
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Partly	People with chronic HCV. This population is subdivided by HCV genotype, previous treatment (treatment-naïve and treatment-experienced), cirrhosis state, and IFN eligibility. This is in line with the scope. Subgroup analyses with post liver transplant patients were not conducted because of a lack of information.
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partly	Excluded: • BOC and TVR Only in scenario analyses: • DCV/SOF/RBV (12/24w) in GT3 cirrhotic patients, • DCV/PR (48w) in GT4 patients, • SMV/PR in GT4 patients, • 2D 24w in GT4 for cirrhotic patients.
Type of economic evaluation	Cost effectiveness analysis	Y	
Perspective on costs	NHS and Personal Social Services (PSS)	Y	
Perspective on outcomes	All health effects on individuals	Y	
Time horizon	Sufficient to capture differences in costs and outcome	Y	Until 100 years of age (in fact lifetime)
Synthesis of evidence in	Systematic review	N	No evidence synthesis is performed (e.g. for SVR), despite there being several sources per treatment and having been requested during the

outcomes			clarification phase by the ERG
Measure of health effects	Quality adjusted life years (QALYs)	Y	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Y	The EQ-5D-3L or the SF-36 health status questionnaire was used to collect HRQoL data in the different HRQoL source used by the company
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Partly	UK TTO valuations have been used as a default for the EQ-5D-3L questionnaire, converting questionnaire responses to utilities which are applied in the economic model in the study from Wright et al., 2006[53] and Ratcliffe et al., 2002[54] while US preference weights have been used in Vera-Llonch et al., 2013[55]
Discount rate	An annual rate of 3.5% on both costs and health effects	Y	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Y	
Sensitivity analysis	Probabilistic modelling	Partly	Probabilistic modelling was applied, but the implementation was incorrect (it was not possible to consider multiple comparators simultaneously).
EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Clinical Excellence; PSA = probablistic sensitivity analysis; quality-adjusted life years; PSS = Personal Social Services; TTO = Time trade off; UK = United Kingdom			

5.2.2 Model structure

The company developed a de novo Markov state transition model to represent the natural history of CHC. The model structure was said to be adapted from the model by Dusheiko and Roberts, 1995.[52] The same model structure was used for all patient subgroups, irrespective of HCV genotype or treatment experience. This model has been further adapted in line with previous Gilead submissions to NICE (TA363, 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 divided into mild and moderate states, or by METAVIR fibrosis score (F0-F4). The company argued that this model structure reflects current UK clinical practice, and offers the best fit for the Gilead pivotal Phase III trials for SOF/VEL, in which patients were split between non-cirrhotic and cirrhotic defined as per the Fibrotest and Fibroscan scores.

Figure 5.1: Model structure (Figure 16 CS)



Note: dashed arrows are only considered in sensitivity analyses; ERG note: the transition from compensated cirrhosis to hepatocellular carcinoma is not depicted.

Patients may be in a non-cirrhotic, compensated cirrhosis or decompensated cirrhosis state at model entry. From decompensated cirrhosis, patients may progress to a liver transplant (tunnel) state and post liver transplant state. From both cirrhosis states patients can progress to the HCC health state. Excess mortality is accounted for from the decompensated cirrhosis, liver transplant and HCC states. Twelve or 24 weeks after active treatment, patients in the non-cirrhotic and (de)compensated cirrhosis states may achieve SVR and move to the corresponding (non) cirrhosis state. Patients in the non-cirrhotic SVR state are considered cured and will not become symptomatic again. All patients experience a background mortality risk, except in the active treatment phase where there is no risk of mortality. The model structure is depicted in Figure 5.1.

The company stated that the model uses a two-week cycle length for the first 72 weeks, followed by one 24-week cycle. Thereafter, transitions occur on an annual basis. The shorter initial cycles allowed the company to model different treatment strategies with patients transiting to a health state with SVR at different cycles. The half-cycle correction was only applied to the annual cycles.

The definitions of the health states are presented in Table 5.4. Patients were classified as non-cirrhotic or compensated cirrhosis based on Fibroscan, Fibrotest and/or METAVIR scores.

Table 5.4: Health state definitions (adapted from Table 60 CS)

State	Definition
Non-cirrhotic	Fibroscan (in countries where locally approved) with a result of ≤12.5 kPa within ≤6 months of Baseline/Day 1† Fibrotest score of ≤0.48 and an APRI of ≤1 performed during screening† METAVIR score < 4
Compensated cirrhosis	Fibroscan (in countries where locally approved) showing cirrhosis or results ≥12.5 kPa† Fibrotest score of >0.75 and an AST: platelet ratio index (APRI) of >2 performed during screening† METAVIR score = 4
Decompensated cirrhosis	Clinical (major symptomatic)‡ & histological (cirrhosis)
SVR – Non-cirrhotic	Virologic, 12/24 weeks after the end of therapy
SVR – Compensated cirrhosis	Virologic, 12/24 weeks after the end of therapy
SVR – Decompensated cirrhosis	Virologic, 12/24 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; kPa, Kilopascal; SVR, Sustained virologic response. † Source: Gilead clinical trials protocols; ‡ Major symptomatic = Encephalopathy, Coagulopathy, Variceal bleed.	

ERG comment: The model figure is not entirely correct; the arrow from compensated cirrhosis to hepatocellular carcinoma is not depicted, but present in the Excel model.

The model structure is conceptually similar to the models that were submitted in previous submissions. According to the ERG the model structure reasonably reflects the key elements of CHC, although some simplifications were made. Not distinguishing between mild and moderate cirrhosis is a structural simplification that might influence the results. Another structural simplification is not accounting for mortality risk or disease progression while patients are in the active treatment phase. The active treatment phase consists of time on and off treatment. The on treatment times differ between treatments in the model. The off treatment phase is always 26 weeks (13 cycles of two

weeks). In the example of SOF/VEL, patients are 12 weeks (six cycles) on treatment and 26 weeks (13 cycles) off treatment (12 weeks before SVR is determined and 14 weeks after SVR is determined). Thus, in total, patients cannot experience mortality or disease progression for 38 weeks. This structural approach lacks face validity, but is generally conservative, as SOF/VEL has a shorter or similar treatment duration than all but one comparator (only LDV/SOF has an treatment duration of eight weeks, thus a period of 34 weeks in which no mortality or disease progression occurs). Therefore, the ERG did not change this in the additional analyses.

Furthermore, the model structure does not account for re-treatment due to re-infection or treatment failure. In clinical practice, patients who do not achieve SVR (who do not respond to the therapy or discontinue treatment due to adverse events) or who are re-infected after SVR, may receive further lines of treatments. Not including reinfection favours all active treatments. According to the ERG, not including reinfection is a violation of good modelling practices as reinfection is part of the disease pathway of CHC. Hence, reinfection will be used in the ERG's analyses. The ERG assumed a annual reinfection probability of 2.4% (standard error: 1.4%) in the non-cirrhotic and (de)compensated cirrhosis states based on a systematic review and meta-analysis by Aspinall et al., 2013.[60]

There are some issues with the shorter initial cycle lengths in the model. After 38 cycles the model has not run for two years, as the company states, but for 98 weeks (37 cycles of two weeks plus one cycle of 24 weeks). In addition, the transition probabilities for the shorter cycles are recalculated from the annual probabilities based on a year consisting of 48 weeks. For the cycles of two weeks the transition probabilities are calculated as 1/24 of an annual probability. For the cycle of 24 weeks the transition probabilities are calculated as ½ of an annual probability. Furthermore, the tunnel state for liver transplant is not adjusted for the shorter cycle lengths. As a consequence, the impact of a liver transplant on QALY (utility and mortality risk) and costs is underestimated for liver transplants that occur during the first 38 cycles (98 weeks) in the model. This simplification lacks face validity, but because it will underestimate the impact of active treatment, and hence can be considered conservative, the ERG did not change this in the additional analyses.

Finally, the choice for a static health state transition model did not allow for the incorporation of effects on the population infection rate. Dynamic modelling approaches could have taken into account interaction between individuals within a population by reflecting the effect of HCV treatment on future transmissions. Hence, the total health benefits of more effective treatments with higher SVR rates may have been underestimated.

5.2.3 Population

The population consists of patients with CHC. These patients are defined by HCV genotype, previous treatment, cirrhosis state, and IFN eligibility. These patients reflect the licensed indication for SOF/VEL and the patient population in the phase II/III SOF/VEL studies. Patients who are post-liver transplant are not modelled separately due to a lack of data.

Table 5.5: Populations in the model (Table 59 CS)

GT	Previous CHC treatment		Non-cirrhotic	Cirrhotic	DCC	IFNi
	Naive	Experienced				
GT1a	X	X	X	X		X
GT1b	X	X	X	X		X
GT1	X	X	X	X		X
GT2	X	X	X	X		X
GT3	X	X	X	X		X
GT4	X	X	X	X		X
GT5	X	X	X	X		
GT6	X	X	X	X		
All genotypes	X	X			X	
CHC, chronic hepatitis C; DCC, Decompensated cirrhosis; GT, genotype; IFNi, interferon-ineligible.						

ERG comment: The population is in line with the scope. Patients who are post-liver transplant were not modelled separately because of a lack of data. The ERG agrees that information on this population is scarce.

5.2.4 Interventions and comparators

SOF/VEL (400/100 mg one daily) is a fixed dose combination of two direct acting antivirals, sofosbuvir and velpatasvir, that is used for 12 weeks. In the decompensated cirrhosis population RBV is added to the intervention. The intervention is described in section 3.2.

The comparators differ per subgroup, based on HCV genotype, previous treatment, cirrhosis state and IFN eligibility. An overview is presented in Table 5.6. The comparator for patients with decompensated cirrhosis (all genotypes) is LDV/SOF/RBV. The comparators BOC and TVR were listed in the scope but excluded from the analyses by the company because these regimens are no longer deemed representative for current clinical practice.

Table 5.6: Overview of comparators per subgroup (based on Tables 63-72 CS)

Subgroups			**Comparators**												
			Regimens not containing RBV/P			**Regimens containing RBV/P**									**BSC**
			3D (12 w)	**DCV/SOF (12w)**	**LDV/SOF (8/12w)**	**2D/RBV (12/24w)**	**3D/RBV (12/24w)**	**DCV/PR (48w)**	**DCV/SOF/RBV (12/24w)**	**LDV/SOF/RBV (12w)**	**PR (24/48w)**	**SMV/PR**	**SOF/PR (12w)**	**SOF/RBV (12/24w)**	**BSC**
GT1	**TN**	**NC**	[a]	X	X		[a]				X	X	X		X
		CC			X		[a]		[b,c]		X	X	X		X
	TE	**NC**	[a]	X	X		[a]				X	X	X		X
		CC			X		[a]		[b,c]		X	X	X		X
GT2	**TN**	**NC**									X			[c]	X

Subgroups			Comparators											
			Regimens not containing RBV/P			Regimens containing RBV/P								BSC
			3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
		CC									X			[c] X	X
	TE	NC									X			X	X
		CC									X			X	X
GT3	TN	NC		[c]							X				X
		CC									X		X		X
	TE	NC		[c]							X		X		X
		CC									X		X		X
GT4	TN	NC		[b,c]		X		[b]			X	[b]			X
		CC			X	[b]		[b]	[b,c]		X	[b]	X		X
	TE	NC		[b]	X	X		[b]			X	[b]			X
		CC			X	[b]		[b]	[b,c]		X	[b]	X		X
GT5 & GT6	TN	NC									X				X
		CC									X		X		X
	TE	NC									X				X
		CC									X		X		X

[a] Only included for GT1a or GT1b; [b] Only included in scenario analyses; [c] Only presented as analyses for IFN ineligible patients

ERG comment: The ERG's clinical expert agreed that BOC and TVR are no longer used in clinical practice.

The comparators DCV/SOF/RBV (12/24w) in GT3 cirrhotic patients, DCV/PR (48w) in GT4 patients, SMV/PR in GT4 patients and 2D 24w in GT4 for cirrhotic patients are listed in the scope, but are only included in scenario analyses. In response to clarification question C8,[28] the company stated that *"two of these treatments (DCV+Peg-IFN+RBV 24/48w in GT4 patients and SIM+Peg-IFN+RBV (RGT)) in GT4 patients are irrelevant to clinical practice in the UK, reflected by their omission from relevant treatment guidelines, as described in Section 3.6 of the company submission",* and *"SOF+DCV+RBV 24w in GT3 cirrhotic patients and ombitasvir/paritaprevir/ritonavir 24w in GT4 cirrhotic patients are always dominated in the model economic analyses given the very high cost"*. According to the ERG, these arguments may apply to other comparators as well. Moreover, dominance in the economic model may change when considering the PAS scheme for all comparators. As a result, the decision to omit these comparators from the base-case analysis seems arbitrary and incorrect.

5.2.5 Perspective, time horizon and discounting

The perspective of the analysis is NHS and PSS. The time horizon is until patients reach 100 years of age (in fact lifetime). Costs and utilities are discounted with 3.5%.

ERG comment: Perspective, time horizon and discounting are according to the NICE reference case and appropriate for this assessment.

5.2.6 Treatment effectiveness and extrapolation

This section is subdivided into treatment independent and treatment dependent transition probabilities.

Treatment independent transition probabilities

The company mainly relied on transition probabilities that were used in previous UK HTAs in their analyses (see Table 5.7). A 'targeted' literature review was performed only for the GT3 transition from non-cirrhotic to compensated cirrhosis (see Appendix 15 of the CS). The US study by Kanwal et al., 2014[61] was selected from this review to inform this transition in the model given its sample size (N=8,837 GT3 patients), as it is the most recent publication, consistent with expert advice and given the pan-genotypic coverage. Moreover, the company noted that there was one study conducted in the UK setting.[62] The company did not use this study because of the small sample size (N=30) and the potential selection bias as it was a paired biopsy group. The company argued that a paired biopsy group is potentially more likely to represent patients who had not experienced disease progression.

It should be noted that the only transition that is dependent on GT status is the transition from the "non-cirrhotic" health state to the "compensated cirrhosis" health state. The other treatment independent transition probabilities were assumed, without justification, to be independent of GT status. Moreover, the transitions from (de)compensated cirrhosis were assumed, without justification, to be dependent on SVR status. Finally, the general population mortality probabilities were applied to all health states.[63]

Table 5.7: Treatment independent transition probabilities (annual) retrieved from CS Table 81

From	To	Annual TP	Source	Comments
Non-cirrhotic	Compensated cirrhosis	GT1 0.0213 GT2 0.0165 GT3 0.0296 GT4 0.0202 GT5 0.0202 GT6 0.0202	[61]	Calculated by company
Compensated cirrhosis	Decompensated cirrhosis	0.0438	[64]	Calculated by company
	Hepatocellular carcinoma	0.0631	[64]	Calculated by company
Compensated cirrhosis SVR	Decompensated cirrhosis	0.0064	[64]	Calculated by company
	Hepatocellular carcinoma	0.0128	[64]	Calculated by company
Decompensated cirrhosis	Hepatocellular carcinoma	0.0631	[64]	Calculated by company
	Liver transplant	0.0220	[65]	
	Death	0.2400	[66]	Could not be retrieved by ERG
Decompensated cirrhosis SVR	Hepatocellular carcinoma	0.0631	Assumption	Assumed same as for DCC without SVR
	Liver transplant	0.0220	Assumption	Assumed same as for DCC without SVR

From	To	Annual TP	Source	Comments
	Death	0.0490	[66]	Could not be retrieved by ERG
HCC	Death	0.4300	[67]	Obtained from[68]
Liver transplant (tunnel state)[a]	Death	0.2100	[69]	Obtained from[68]
Post liver transplant[b]	Death	0.0570	[69]	Obtained from[68]

Abbreviations: SVR, Sustained virologic response; TP, Transition probability
[a]Surviving patients will transit to the post-liver transplant health state
[b]This transition probability was not presented in Table 81 of the CS and hence the ERG retrieved this probability from the economic model

ERG comment: The company performed a 'targeted' literature review to identify the transition probability from non-cirrhotic to compensated cirrhosis. However, this search was not considered adequate by the ERG (see Appendix 3 for more details).

For the other transition probabilities the company relied on previous models published in the literature. The ERG disagrees with this approach as preferably systematic searches should be performed to select all transition parameters. Moreover, the selection of all input parameters should be justified (instead of solely referring to the source): this includes justifying the company's approach not to synthesise different sources. Some of the sources selected by the company are approximately 20 years old,[67, 69] and it is unclear whether these are still the most plausible sources. Also, it is unclear how the company calculated some of the transition probabilities in Table 5.7 (see "calculated" in the last column) and why the assumptions made are appropriate (e.g. why data from patients with several liver-related complications can be used for patients with decompensated cirrhosis). Particularly the transition probabilities from compensated cirrhosis to decompensated cirrhosis and from (de)compensated cirrhosis to hepatocellular carcinoma seem high compared with transition probabilities from previous economic evaluations (see Table 32 in Shepherd et al., 2007[68]). After checking the transition probabilities calculated by the company based on literature,[61, 64] it seemed that the calculation was incorrect as the ERG calculated different transition probabilities, which were used in the ERG base-case (see Table 5.8). Moreover, it is unclear why the company believes it is plausible to assume that all but one transition probabilities are independent of GT status. Also, the SVR status dependent transition probabilities for (de)compensated cirrhosis require further justification/details given that SVR is the only treatment dependent probability, i.e. a potential driver of the clinical differences between treatments in the model. Particularly regarding the death probability for decompensated cirrhosis with and without SVR since this is inconsistent with previous assessments and the ERG could not retrieve the transition probability from the source (conference proceedings) provided by the company.[66] It should however be noted that the mortality probability for decompensated cirrhosis with SVR is only used in the analyses for decompensated cirrhosis.

In conclusion, it is unclear to the ERG whether the transition probabilities used by the company are based on the most plausible sources and/or assumptions. Unfortunately, due to time constraints the ERG was unable to perform systematic searches to identify more appropriate transition probabilities. However, given that these transition probabilities were treatment independent, the ERG does not consider this to be a priority issue, except for the SVR status dependent transition probabilities as these might drive the differences between the different treatments.

Table 5.8: Treatment independent transition probabilities (annual) corrected by ERG

From	To	Population	Rate per person-year (95%CI)	Annual TP
Non-cirrhotic	Compensated cirrhosis	GT1[61]	0.0215 (0.0211-0.0219)	0.0217
		GT2[61]	0.0166 (0.0156-0.0177)	0.0167
		GT3[61]	0.0300 (0.0282-0.0318)	0.0305
		GT4-6[61]	0.0204 (0.0168-0.0247)	0.0206
Compensated cirrhosis	Decompensated cirrhosis	GT1-6[64]	0.0416 (0.0273-0.0559)	0.0425
	Hepatocellular carcinoma	GT1-6[64]	0.0585 (0.0423-0.0747)	0.0603
Compensated cirrhosis SVR	Decompensated cirrhosis	GT1-6[64]	0.0063 (0.0000-0.0128)	0.0063
	Hepatocellular carcinoma	GT1-6[64]	0.0125 (0.0028-0.0220)	0.0125
Decompensated cirrhosis[b]	Hepatocellular carcinoma	GT1-6[64]	0.0585 (0.0423-0.0747)	0.0631

Abbreviations: SVR, Sustained virologic response; 95%CI, 95% confidence interval; TP, Transition probability
[a]The rate per person-year (r) was converted to an annual transition probability (TP) using the following formula: TP = - LN(1 - r)
[b]This transition probability was also assumed for decompensated cirrhosis with SVR (consistent with the assumptions made by the company)

Treatment dependent transition probabilities

SVR was the only treatment dependent transition probability used in the model and hence the main driver of clinical differences between the treatments. Nevertheless, the SVR transition probabilities were not described in detail nor justified in the cost effectiveness chapter of the CS. The actual SVR probabilities were only described in the "summary of base-case de novo analysis inputs" section of the CS. Table 5.9 provides an overview of SVR probabilities, retrieved based on naïve comparisons and used in the economic model. Although not explicitly stated in the CS, for BSC a SVR of 0% was used (found within the Excel model by the ERG).

Table 5.9: SVR (percentage) retrieved from CS Section 5.6.1

				Regimens not containing RBV/P				Regimens containing RBV/P								BSC
				SOF/VEL (12w)[a]	3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC[d]
GT1a	TN	non-CC	SVR	97.5[32]		100.0[70]	94.0[44]		97.0[71]				43.6[72]	82.0[73, 74]	91.7[58]		0.0
		CC	SVR	100.0[32]			94.1[56]		92.9[75]		100.0[76]		23.6[72]	60.4[73, 74]	80.8[58]		0.0
	TE	non-CC	SVR	97.5[32]		100.0[70]	95.4[57]		96.0[77]				17.6[78]	80.1[73, 74]	74.0[c]		0.0
		CC	SVR	100.0[32]			86.4[57]		95.4[75]		98.5[76]		10.0[78]	74.4[73, 74]	74.0[c]		0.0
GT1b	TN	non-CC	SVR	100.0[32]	99.0[71]	100.0[70]	94.0[44]						43.6[72]	82.0[73, 74]	91.7[58]		0.0
		CC	SVR	95.8[32]			94.1[56]		100.0[75]		100.0[76]		23.6[72]	60.4[73, 74]	80.8[58]		0.0
	TE	non-CC	SVR	100.0[32]	100.0[79]	100.0[70]	95.4[57]						17.6[78]	80.1[73, 74]	74.0[c]		0.0
		CC	SVR	95.8[32]			86.4[57]		97.8[75]		98.5[76]		10.0[78]	74.4[73, 74]	74.0[c]		0.0
GT1	TN	non-CC	SVR	98.4[e]		100.0[e]	94.0[e]						43.6[e]	82.0[e]	91.7[e]		0.0
				98.5[e]			94.1[e]		95.4[e]-		100.0[e]		23.6[e]	60.4[e]	80.8[e]		0.0
		CC	SVR						100.0[e]								
	TE	non-CC	SVR	98.4[e]		100.0[e]	95.4[e]						17.6[e]	80.1[e]	74.0[e]		0.0
		CC	SVR	98.5[e]			86.4[e]				100.0[e]		10.0[e]	74.4[e]	74.0[e]		0.0
GT2	TN	non-CC	SVR	99.0[31]									80.6[31, 58]			95.8[31]	0.0
		CC	SVR	100.0[31]									71.5[31, 58]			93.3[31]	0.0
	TE	non-CC	SVR	100.0[31]									35.0[80, 81]			81.3[31]	0.0
		CC	SVR	100.0[31]									35.0[80, 81]			100.0[31]	0.0
GT3	TN	non-CC	SVR	98.2[31]		77.8[17, 69]							71.2[82]		95.8[83]	90.4[31]	0.0
		CC	SVR	93.0[31]							57.9[f]		29.7[82]		91.3[83]	73.3[31]	0.0
	TE	non-CC	SVR	91.2[31]		71.4[17, 69]							35.0[80, 81]		94.2[83]	71.0[31]	0.0
		CC	SVR	89.2[31]							69.2[f]		35.0[80, 81]		85.7[83]	57.9[31]	0.0
				96.6-			94.4-	100.0[86]		81.2[87]			45.0[87]	84.4[88]	100.0[58]		0.0
GT4/5/6	TN	non-CC	SVR	100.0[32]			100.0[84, 85]										
				100.0[32]			83.3-	100.0[86]		77.8[87]			25.0[87]	66.7[88]	50.0[58]		0.0
		CC	SVR				100.0[84, 85]										
	TE	non-CC	SVR	100.0[32]			84.6[84]	100.0[86]		81.2[f]			45.0[f]	63.6[88]	100.0[58]		0.0

		Regimens not containing RBV/P				Regimens containing RBV/P									BSC
		SOF/VEL (12w)[a]	3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC[d]
CC	SVR	100.0[32]			100.0[84]	100.0[86]		77.8[f]			25.0[f]	46.4[88]	50.0[58]		0.0
DCC[b]	SVR	94.3[33]							86.4[89]						

Abbreviations: TN, treatment naïve; TE, treatment experienced; SVR, sustained virologic response; DCC, Decompensated cirrhotic
[a]For DCC this is SOF/VEL/RBV
[b]Identical for TN and TE
[c]FDA analysis
[d]BSC SVR of 0% is based on an assumption
[e]Source not presented by the company
[f]Based on assumptions made by the company

ERG comment: Consistent with the critiques raised in section 4.4, more justification and explanations are needed regarding the seemingly arbitrary selection of sources and the subsequent selection of SVR rates from those sources. Using only one source for the SVR rate for each intervention and population increases the chance of bias and cherry-picking. Additionally, the company did not provide sensitivity analyses to show the impact of other sources for SVR rates on the results.

5.2.7 Health related quality of life

The SF-36 was administered in the ASTRAL trials,[31-33] but SF-6D utility scores were not presented. Consequently, the health related quality of life estimates in the company's cost effectiveness analysis were based on literature. The company performed a systematic literature review and concluded that Wright et al., 2006[53] was the most suitable source to retrieve health related quality of life data for the current decision problem. The utility value for the 'non-cirrhotic' health state in the current assessment is a weighted average of the 'mild' and 'moderate HCV disease' health state utility values reported in Wright et al., 2006[53] The assumed proportion of 'mild' and 'moderate' HCV patients is respectively 83% and 17%. No reference was provided for these figures.

The company added a utility increment of 0.04 to the health state utility values of patients who had achieved a SVR (i.e. in the following health states: 'non-cirrhotic with SVR', 'compensated cirrhosis with SVR', and 'decompensated cirrhosis with SVR'). This utility increment was retrieved from Vera-Llonch et al., 2013[55] According to the company, this study was the most recent study reporting on SVR quality of life benefit. This SVR estimate was also considered as the *"least uncertain"*.[1] Health state utility values are provided in Table 5.10.

Table 5.10: Utility values used in the company's base-case analysis (adapted from CS, Table 82)

Health-state	Utility	Source
Baseline – non-cirrhotic	0.75*	Wright et al., 2006[α 53]
Baseline – compensated cirrhosis	0.55*	
Baseline - decompensated cirrhosis	0.45*	Ratcliffe et al. (2002)[β 54]
Hepatocellular carcinoma	0.45	
Liver transplant	0.45	
Post-liver transplant	0.67	

* SVR utility increment (0.04) is added to these health state utility values when patients are in one of the following health states: 'Non-cirrhotic with SVR', 'Compensated cirrhotic with SVR', 'Decompensated cirrhotic with SVR'

[α] Reported by the company in the CS

[β] Primary source as reported in Wright et al., 2006[53], added by the ERG. Reported as Wright et al., 2006[53] in the CS

In addition, utility increments or decrements were applied to the utility values of the health states 'non-cirrhotic', 'compensated cirrhosis', and 'decompensated cirrhosis' when patients were receiving active treatment (the 'on-treatment' period), to represent the impact of treatment and treatment-related adverse events on quality of life. On-treatment utility increments and decrements were treatment specific and multiplicatively applied to the health state utility values. Therefore, these utility increments and decrements are expressed as percentages. The on-treatment utility increment of SOF/VEL was assumed to be equal to the on-treatment utility increment of LDV/SOF because of the unavailability of utility values from the ASTRAL trials[31-33] at the time of submission. LDV/SOF

utility values were based on the ION trials,[44, 56, 57] in which utilities were elicited based on the SF-36 and converted to the SF-6D. FISSION, FUSION and NEUTRINO are the remaining sources of on-treatment utility increments and decrements.[58, 59] In these studies, the SF-36 was also used and then converted to the SF-6D (Table 5.11).

Table 5.11: On-treatment utility increments and decrements for each subgroup (in percentage) (adapted from CS, Tables 93, 97, 103, 104, 108, 112, 116, 120,124 and 128)

Subgroups			**Comparators**														
			SOF/VEL (12w)	2D/RBV (12w)	2D/RBV (24w)	3D (12 w)	3D/RBV (12w)	3D/RBV (24w)	DCV/SOF (12w)	DCV/SOF/RBV (12/24w)	LDV/SOF (8/12w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	SOF/VEL/RBV (12w)
GT1/1a/1b	TN	non-CC	4.43			4.43	-3.25		4.43		4.43		-14.77	-14.27	-14.52		
		CC	4.43				-3.25	-1		4.43	4.43						
	TE		4.43			4.43	-3.25	-1	4.43		4.43		-14.77	-14.61	-14.52		
GT2*	TN		4.43										-14.77			-2.55	
	TE		4.43										-14.77			-6.88	
GT3*	TN		4.43						4.43	-3.25			-14.77		-14.52	-2.55	
	TE		4.43						4.43	-1			-14.77		-14.52	-6.88	
GT4/5/6*	TN		4.43	-3.25	-1						4.43		-14.77		-14.52		
	TE		4.43	-3.25	-1						4.43		-14.77		-14.52		
DCC			4.43									-3.25					-3.25

GT= genotype; TN= treatment-naïve; TE= treatment-experienced; CC = cirrhotic; DCC = decompensated cirrhosis
* No difference made between cirrhotic and non-cirrhotic

ERG comment: The ERG had concerns about the non-use of health related quality of life evidence from the ASTRAL trials,[31-33] the source used for health state utility values, the proportion of 'mild' and 'moderate' HCV patients to calculate the 'non-cirrhotic' health state utility value, the sources used for the SVR utility increment, the use of SVR increment for the 'compensated cirrhosis with SVR' and 'decompensated cirrhosis with SVR' health states and the implementation of the on-treatment utility increments and decrements.

Since the SF-36 as administered in the ASTRAL trials,[31-33] the ERG requested the company to provide a sensitivity analysis in which these SF-36 values were converted in SF-6D utility values. The company did not meet this request. The ERG considers the use of utility values from the literature instead of the collected evidence from the ASTRAL trials[31-33] as a second-best option.

In addition, the ERG asked the company to justify its choice for Wright et al., 2006[53] as a source for health state utility values. The company responded that it was the only study identified in the systematic literature review that provided high quality EQ-5D utility values for the UK (see Appendix 3 for the ERG critique on the health related quality of life literature review). Wright et al., 2006 is an RCT and economic evaluation assessing the effectiveness and cost effectiveness of IFN-alfa-2b with RBV versus no treatment in patients diagnosed with mild HCV.[53] The utility value for the 'mild disease' health state in Wright et al., 2006's economic evaluation (part of the 'non-cirrhotic' health state in the current assessment) was directly elicited during the trial reported in Wright et al., 2006[53]. Patients for this trial were assessed for recruitment between 1998 and 2000. For the 'moderate disease' health state in Wright et al.'s economic evaluation (part of the 'non-cirrhotic' health state in the current assessment), utility values were obtained from a single EQ-5D measurement. This utility elicitation took place in 2002 and was also performed and reported in Wright et al., 2006[53] The health state utility values for the more advanced stage of the disease reported in Wright et al., 2006 (based on Ratcliffe et al., 2002[54]) were taken from an observational research assessing the quality of life of patients considered for liver transplant. This study took place between 1996 and 1998.[54] The utility values reported in Wright et al., 2006[53] were consequently elicited from studies dating from 1996 to 2002. According to the ERG, the evidence collected in the ASTRAL trials[31-33] may have been more representative for the current decision problem because general practices in HCV treatment have changed through the introduction of DAAs.

The utility value for the 'non-cirrhotic' health state was based on a weighted average of mild (83%) and moderate (17%) HCV patients. These proportions were not underpinned with evidence. In response to clarification question C14, the company explained, that these proportions were obtained from *HCV TherapyWatch market research data*, a physician survey conducted by Gilead Science.[28] The ERG was not able to assess the validity of these figures because of the lack of transparency in the description of the methods used (e.g. the number of physicians who took part in the research; the discrepancies in the reported proportions of patients having mild/moderate HCV between physicians).

The utility increment for achieving a SVR was obtained from Vera-Llonch et al., 2013.[55] In this study, the EQ-5D and US-valuation weights were used to assess the impact on quality of life of 12-week TVR with 24 or 48 weeks PR, or 48 weeks of PR in genotype 1 treatment naïve HCV patients. This utility increment is however obtained from US EQ-5D tariffs and might not be representative of UK preferences. The SVR utility increment reported in Wright et al., 2006 is higher (0.05).[53] Insight into the SVR utility increment as observed in the ASTRAL trials[31-33] would have been helpful to reduce uncertainty regarding this model input estimate.

Furthermore, the company does not provide a justification for the application of a SVR utility increment in the 'compensated cirrhosis with SVR' and 'decompensated cirrhosis with SVR' health states. Previous TA's[13, 16-18] included a utility increment for patients with compensated cirrhosis who achieved a SVR, although this is not supported by the results from Wright et al., 2006[53]. Neither previous TA's[13, 14, 16-18] nor Wright et al., 2006[53] included a utility increment for patients with decompensated cirrhosis who achieved a SVR. The ERG judges this latter approach as most plausible and will consequently not include a SVR utility increment for patients with decompensated cirrhosis who have achieved a SVR.

Finally, the ERG requested clarification on the evidence supporting on-treatment utility increments and decrements and on the choice for a multiplicative implementation of those.[27] No additional justification was provided for the choice of on-treatment utility increments and decrements values (clarification question C12)[28] and the multiplicative approach was justified by referring to Ara and Wailoo, 2013[90] who consider the multiplicative approach acceptable. The ERG agrees that a multiplicative approach might be suitable but uncertainty remains whether this is the optimal choice in the current context. As the on-treatment utility increments and decrements are predominantly based on assumptions (CS, Tables 93, 97, 103, 104, 108, 112, 116, 120,124 and 128[1]) the ERG considers these estimates uncertain. Nevertheless, the ERG agrees that the on-treatment utility increments and decrements seem to reflect the direction of the effect of the different treatments on quality of life. The ERG acknowledges, and agrees with the company, that applying utility increments and decrements do not sensibly affect the results (response to the clarification letter Tables 35 to 38).[28]

5.2.8 Resources and costs

A systematic review of the literature was performed to identify any additional resource data published since the SOF and LDV/SOF NICE submissions.[25] The company did not identify any additional relevant sources. Hence, sources and values from previous SOF and LDV/SOF submissions[16, 91] were used, inflated to the 2014/2015 cost year using the HCHS Pay and Prices Index.[92] In addition, the systematic review updates of cost effectiveness evaluations and HRQoL extracted data from UK-based studies, which were analysed to identify any additional relevant resources for use in the economic model. NHS reference costs were used for the unit costs of managing patients while on treatment.[93] Costs were inflated to 2014/2015 values.

Drug costs

Estimates for comparators were obtained from the British National Formulary (March 2016).[94] The drug costs (cost per pack and week costs) are presented in Table 5.12. These weekly drug costs are multiplied by the treatment duration (incorporating treatment discontinuation) as presented in section 5.6.1 of the CS.[1]

Table 5.12: Treatment unit costs (CS Table 83)

Drug	Cost per pack	Unit dose	Quantity/ pack	Weekly costs[a]	Source	Assumption
SOF/VEL	£12,993.33 (Anticipated list price) [redacted]	500 mg	28	£38,980 (Anticipated list price) [redacted]	Gilead	Fixed price-CIC
LDV/SOF	£12,993.33	490 mg	28	£3,248	BNF, 23rd March	

Drug	Cost per pack	Unit dose	Quantity/ pack	Weekly costs[a]	Source	Assumption
					2016[94]	
SOF	£11,660.98	400 mg	28	£2,915	BNF, 23rd March 2016[94]	
RBV	£246.65	400 mg	56	£92	BNF, 23rd March 2016[94]	Copegus® 400mg Tablet
PR	£124.40	180 µg	1	£124	BNF, 23rd March 2016[94]	Pegasys® Syringe
DCV	£8,172.61	60 mg	28	£2,043	BNF, 23rd March 2016[94]	Daklinza® 60mg tablets
2D	£10,733.33	275 mg	28	£2,683	BNF, 23rd March 2016[94]	Viekirax 275mg tablets
DSV	£933.33	250 mg	56	£233	BNF, 23rd March 2016[94]	Exviera 250mg tablets
SMV	£1,866.50	150 mg	7	£1,867	BNF, 23rd March 2016[94]	Olysio 150mg tablets

Abbreviations: 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

[a]Weekly dose and costs were retrieved by the ERG from the economic model

Monitoring costs

The costs of monitoring patients while they are on treatment with either SOF/VEL or a comparator were estimated according to resource use following Shepherd et al., 2007.[68] The unit costs used to estimate the monitoring costs are displayed in Table 84 of the CS;[1] costs were inflated to 2014-2015 when more recent ones were not available. Table 5.13 provides an overview of the monitoring costs during active treatment. Additionally, the model included costs for the initial evaluation of a new patient with confirmed HCV (£636 for non-cirrhotic and £831 for cirrhotic patients) as well as further investigation costs (£476). Finally, surveillance costs for patients who are unsuitable for P were incorporated (£107 for non-cirrhotic and £338 for cirrhotic patients).

Table 5.13: Monitoring costs during active treatment

	Weeks of treatment	**PR**	**SMV/PR**	**Other (excl final visit)**	**Other (incl final visit)**
Total non-cirrhotic	4	[redacted]	£695	£598	£598
	6	[redacted]	£807	£598	£987
	8	[redacted]	£923	£710	£987
	12	[redacted]	£1,324	£822	£1,099
	16	[redacted]	£1,436	£934	£1,211
	24	[redacted]	£1,796	£1,323	£1,323
	28	[redacted]	£1,964	NA	NA

	Weeks of treatment	PR	SMV/PR	Other (excl final visit)	Other (incl final visit)
	36	[redacted]	£2,208	NA	NA
	48	[redacted]	£2,680	NA	NA
Total cirrhotic	4	[redacted]	£695	£598	£598
	6	[redacted]	£807	£598	£988
	8	[redacted]	£923	£710	£988
	12	[redacted]	£1,438	£822	£1,100
	16	[redacted]	£1,662	£934	£1,212
	24	[redacted]	£2,255	£1,324	£1,324
	28	[redacted]	£2,423	NA	NA
	36	[redacted]	£2,781	NA	NA
	48	[redacted]	£3,749	NA	NA
Abbreviation: NA, not applicable					

Health-state costs and resource use

Health state costs (Table 5.14) were assumed to be independent of the monitoring costs because these are applied in health states outside of treatment.

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 Grishchenko et al., 2009.[95] 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;[53] the costs for the liver transplantation were obtained from Longworth et al., 2014.[96] 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[96] 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 provided in Wright et al., 2006.[53] Costs of non-cirrhotic and cirrhotic patients who reached a SVR were from Grishchenko et al., 2009[95] because the costs collected from the UK mild hepatitis C RCT (which were used by Shepherd et al., 2007[68] and Hartwell et al., 2011[97]) did not split between non-cirrhotic and cirrhotic patients. Costs of decompensated cirrhosis with SVR were conservatively assumed to be the same as those without SVR. All costs have been updated to 2014/2015 costs using the HCHS Pay and Prices Index.[92]

Table 5.14: Health state costs

Health state costs	Inflated-values to 2014-2015	Source
Non-cirrhotic, mild	£189	Wright et al., 2006[53]
Non-cirrhotic, moderate	£1,001	Wright et al., 2006[53]
Non-cirrhotic[a]	£327	Calculation
Non-cirrhotic with SVR (mild)	£237	Grishchenko et al., 2009[95]
Non-cirrhotic with SVR (moderate)	£290	Grishchenko et al., 2009[95]
Non-cirrhotic with SVR[a]	£246	Calculation
Compensated cirrhosis	£1,561	Wright et al., 2006[53]

Health state costs	Inflated-values to 2014-2015	Source
Compensated cirrhosis with SVR	£513	Grishchenko et al., 2009[95]
Decompensated cirrhosis	£12,510	Wright et al., 2006[53]
Decompensated cirrhosis with SVR	£12,510	Assumed same as decompensated cirrhosis from Wright et al., 2006[53]
HCC	£11,147	Wright et al., 2006[53]
Liver transplant	£85,191	Longworth et al., 2014[96]
Post-liver transplant follow-up phase (0-12 months)	£28,067	Longworth et al., 2014[96]; Split between post-liver transplant year 1 and year 2 cost based on Wright et al., 2006[53]
Post-liver transplant follow-up phase (12-24 months)	£4,194	
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		

Adverse reaction unit costs and resource use

The adverse events management costs are presented in Table 5.15. The management costs were calculated based on adverse event drug unit costs (CS Table 87), adverse event drug treatment dosing and duration (CS Table 88) and outpatient, GP and specialist costs (CS Table 89). No inpatient costs were considered because most of these adverse events are treated during outpatient visits, according to expert opinion.

Table 5.15: Adverse event costs (costs per episode)[a]

AE	Costs
Nausea	£2.49
Vomiting	£2.49
Diarrhoea	£1.84
Pruritus	£3.36
Rash	£611.95
Anaemia (Epo)	£10.50
Anaemia (blood transfusion)	£8.04
Thrombocytopenia	£1,897.67
Neutropenia	£1,329.11
Depression	£110.35
[a]Retrieved by the ERG from the economic model	

ERG comment: Regarding the monitoring costs, it is unclear why the company calculated these with and without 'final visit' and why the company opted to use the cost estimate excluding the 'final visit' in most cases in the model. Moreover, the use of Shepherd et al., 2007[68] to calculate the monitoring costs was not justified. In the ERG additional analyses, the ERG included the final visit for all comparators.

All health state costs except for the costs associated with liver transplant seem reasonable, particularly given that the company used a systematic review to identify sources and justifications were provided for selection of the most plausible source. The liver transplant costs are much higher than costs mentioned in other sources. For instance, the costs mentioned in Longworth et al., 2003[98] range from £52,525 to £66,049 depending on the population. But these costs are not specific for HCV patients,

whereas the source used by the company is a report on costs of liver transplant in HCV and HBV commissioned by the company,[96] based on the CELT study and expert opinion. Although this source is not peer-reviewed, the ERG acknowledges that this estimate might be the best available. Additionally, also the treatment and adverse event costs are considered reasonable by the ERG.

5.2.9 Cost effectiveness results

The company base-case results presented in Tables 129-170 of the CS are summarised in Table 5.16. In most subgroups, SOF/VEL was more effective (in terms of QALYs) than the other compactors, exceptions being in all subgroups with DCV/SOF (12w) and some of the subgroups with LDV/SOF (8/12w), SOF/PR (12w) and SOF/RBV (12/24w). Additionally, SOF/VEL is also more expensive than 2D/RBV (12/24w), PR (24/48w), SMV/PR and BSC while SOF/VEL is less expensive than DCV/SOF (12w), LDV/SOF/RBV (12w) and SOF/RBV (12/24w). For the other comparisons this was dependent on the subgroup considered.

It should be noted that on some occasions the (anticipated) list price was used by the company (instead of the discounted price). Moreover, some comparators were only presented in scenario analyses and/or only for IFN-ineligible subgroups.

For a willingness to pay of £20,000 and £30,000 per QALY, SOF/VEL was in general cost effective compared to most comparators. However, based on a willingness to pay of £20,000 and £30,000, SOF/VEL (anticipated list price) was not cost effective compared to LDV/SOF (GT1 TN non-cirrhotic) and 2D/RBV (GT4 TN and TE non-cirrhotic). Moreover, based on a willingness to pay of £20,000 and £30,000, SOF/VEL (discounted price) was not cost effective compared to PR (GT2 TN non-cirrhotic).

Table 5.16: Company base-case results (discounted price for SOF/VEL unless stated otherwise) retrieved from CS Tables 129-170[a]

				Totals	Increments versus SOF/VEL (12w)[b]											
					Regimens not containing RBV/P			Regimens containing RBV/P								BSC
				SOF/VEL (12w)[b]	3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT1	**TN**	**non-CC**	**Costs**	£41,829[c]	[d]	-£20,554	**£12,116**		[d]				£20,949	£8,012	£498		£25,525
			QALYs	17.27		-0.05	**0.17**						2.05	0.66	0.29		3.64
			iCER			£411,080	**£71,271**						£10,219	£12,139	£1,717		£7,012
		CC	**Costs**	£59,495[c]			-£854		[d]		[e,f]		£15,918	£3,670	-£1,519		£23,705
			QALYs	10.11			0.23						3.75	1.95	0.95		5.13
			iCER				Dom						£4,245	£1,882	Dom		£4,621
	TE	**non-CC**	**Costs**	£41,176[c]	[d]	-£20,571	-£715		[d]				£19,764	£2,639	-£1,993		£25,844
			QALYs	16.27		-0.05	0.10						2.61	0.68	0.82		3.19
			iCER			£411,420	Dom						£7,572	£3,881	Dom		£8,102
		CC	**Costs**	£57,869[c]			-£2,419		[d]		[e,f]		£15,469	£350	-£2,774		£22,508
			QALYs	9.71			0.59						4.16	1.11	1.21		4.78
			iCER				Dom						£3,719	£315	Dom		£4,709
GT2	**TN**	**non-CC**	**Costs**	[redacted]									**£20,729**			[f]	£16,210
			QALYs										**0.63**				3.12
			iCER										**£32,903**				£5,196
		CC	**Costs**	[redacted]									£18,094			[f]	£12,619
			QALYs										1.46				5.20
			iCER										£12,393				£2,427
	TE	**non-CC**	**Costs**	[redacted]									£11,378			-£10,595	£16,394
			QALYs										1.82			0.53	2.77
			iCER										£6,252			Dom	£5,918
		CC	**Costs**	[redacted]									£7,740			-£8,154	£11,490
			QALYs										3.00			-0.01	4.83
			iCER										£2,580			£1.6 mil	£2,379
GT3	**TN**	**non-CC**	**Costs**	[redacted]		[f]							£18,958				£12,590
			QALYs										1.24				4.41
			iCER										£15,289				£2,855

				Totals	Increments versus SOF/VEL (12w)[b]												
					Regimens not containing RBV/P			Regimens containing RBV/P									BSC
				SOF/VEL (12w)[b]	3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
		CC	Costs	[redacted]							[f]		£12,612		-£9,917	[f]	£14,020
			QALYs										3.24		0.11		4.84
			iCER										£3,893		Dom		£2,897
	TE	non-CC	Costs	[redacted]		[f]							£10,556		-£8,734		£14,144
			QALYs										2.21		-0.08		3.61
			iCER										£4,776		£109,175		£3,918
		CC	Costs	[redacted]							[f]		£9,766		-£9,857	[f]	£13,516
			QALYs										2.50		0.19		4.33
			iCER										£3,906		Dom		£3,121
GT4	TN	non-CC	Costs	£41,682[c]		[e,f]		**£5,490**		[e]			£21,172	[e]			£25,726
			QALYs	17.32				**0.01**					2.00				3.57
			iCER					**£549,000**					£10,586				£7,206
		CC	Costs	[redacted]			-£10,326	[e]		[e]	[e,f]		£5,268	[e]	-£18,223		£12,820
			QALYs				0.00						3.75		2.60		5.20
			iCER				Dom						£1,405		Dom		£2,465
	TE	non-CC	Costs	£41,046[c]		[e]	-£1,757	**£5,490**		[e]			£21,704	[e]			£26,048
			QALYs	16.32			0.48	**0.01**					1.76				3.14
			iCER				Dom	**£549,000**					£12,332				£8,296
		CC	Costs	[redacted]			-£10,317	[e]		[e]	[e,f]		£5,001	[e]	-£18,408		£11,617
			QALYs				0.00						3.49		2.43		4.85
			iCER				Dom						£1,433		Dom		£2,395
GT5	TN	non-CC	Costs	[redacted]									£10,958				£15,512
			QALYs										1.88				3.45
			iCER										£5,829				£4,496
GT6	TN	non-CC	Costs	[redacted]									£10,438				£14,992
			QALYs										2.00				3.57
			iCER										£5,219				£4,199
GT5/6[g]	TN	CC	Costs	[redacted]									£5,268		-£18,223		£12,820
			QALYs										3.75		2.60		5.20
			iCER										£1,405		Dom		£2,465

				Totals	Increments versus SOF/VEL (12w)[b]											
					Regimens not containing RBV/P			Regimens containing RBV/P								BSC
				SOF/VEL (12w)[b]	3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
	TE	non-CC	Costs	[redacted]									£10,969				£15,313
			QALYs										1.76				3.14
			iCER										£6,232				£4,877
		CC	Costs										£5,001		-£18,408		£11,617
			QALYs										3.49		2.43		4.85
			iCER										£1,433		Dom		£2,395
DCC	TN		Costs									-£7,329					
			QALYs									0.16					
			iCER									Dom					
	TE		Costs									-£7,493					
			QALYs									0.15					
			iCER									Dom					

Abbreviations: TN, treatment naïve; TE, treatment experienced; Dom, dominance; iCER, incremental cost-effectiveness ratio; mil, million;

[a]To be consistent with the results presented in the CS, the incremental costs, QALYs and ICERs were recalculated by the ERG from the results presented in the CS. As a result, rounding errors might be induced. In addition, after consulting a clinical expert it was decided not to present the results for GT1a and GT1b but to present the results for the combined GT1 group only. This was done as it is consistent with the final scope and for reading convenience, given the amount of subgroups and comparators considered. Although there is some evidence of a differential response for GT1a and GT1b, this difference is small in magnitude and is unlikely to be a major issue from a clinical perspective.

[b]For DCC this is SOF/VEL/RBV

[c]Based on (anticipated) list price for SOF/VEL

[d]Only included for GT1a and/or GT1b by the company

[e]Only included in scenario analyses by the company

[f]Only presented by the company in the analysis for IFN ineligible patients

[g]The results for GT5 and GT6 were in part combined since these were identical.

ERG comment: The ERG noticed several inconsistencies between the total costs for SOF/VEL presented in the CS and the results obtained in the model for GT1 and GT4. This is corrected in Table 5.17. For clarity, the sensitivity analyses and analyses for the IFN-ineligible subgroups are incorporated in this overview. Moreover, the 3D comparator (with or without RBV) was only reported for GT1a and GT1b respectively (not for the combined GT1 group). Therefore, for the combined GT1 group, 3D without RBV was retrieved from the GT1b subgroup (unavailable for GT1a) and 3D/RBV was retrieved from GT1a (as this was available for all four subgroups for GT1a). This assumption is supported by the notion that all treatment independent transition probabilities are equal for GT1, GT1a and GT1b. Additionally, in Table 5.17, the anticipated list price for SOF/VEL is used in the analyses for GT1, GT3 and GT4 as DCV and/or ombitasvir are included in these analyses.

Based on the corrected overview in Table 5.17, for a willingness to pay of £20,000 and £30,000 per QALY, SOF/VEL was cost effective compared to most comparators. However, based on a willingness to pay of £20,000 and £30,000, SOF/VEL (anticipated list price) was not cost effective compared to:

- 3D (GT1 TN and TE non-cirrhotic);
- LDV/SOF (GT1 TN non-cirrhotic, GT4 TN and TE cirrhotic);
- 2D/RBV (GT4 TN and TE non-cirrhotic);
- 3D/RBV (GT1 TN and TE non-cirrhotic)
- DCV/PR (GT4 TN non-cirrhotic) and;
- PR (GT3 TN non-cirrhotic) – only for a willingness to pay of £20,000.

Finally, based on a willingness to pay of £20,000 and £30,000, SOF/VEL (discounted price) was not cost effective compared to PR (GT2 TN non-cirrhotic).

Table 5.17: Company base-case results (discounted price for SOF/VEL unless stated otherwise) retrieved from CS Tables 129-170 and 225-238 and corrected by the ERG[a]

				Totals	Increments versus SOF/VEL (12w)[b]												
					Regimens not containing RBV/P			Regimens containing RBV/P									BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT1	**TN**	**non-CC**	**Costs**	£42,008[g]	**£4,500**	-£20,375	**£12,295**		**£2,907**				£21,128	£8,191	£677		£25,704
			QALYs	17.27	**-0.02**	-0.05	**0.17**		**0.07**				2.05	0.66	0.29		3.64
			iCER		**Dom**	£407,500	**£72,324**		**£41,529**				£10,306	£12,411	£2,334		£7,062
		CC	**Costs**	£59,674[g]			-£675		-£32,452		-£21,556[e]		£16,097	£3,849	-£1,340		£23,884
			QALYs	10.11			0.23		0.27		0.88[e]		3.75	1.95	0.95		5.13
			iCER				Dom		Dom		Dom[e]		£4,293	£1,974	Dom		£4,656
	TE	**non-CC**	**Costs**	£41,356[g]	**£4,110**	-£20,391	-£535		**£2,746**				£19,944	£2,819	-£1,813		£26,024
			QALYs	16.27	**-0.05**	-0.05	0.10		**0.09**				2.61	0.68	0.82		3.19
			iCER		**Dom**	£407,820	Dom		**£30,511**				£7,641	£4,146	Dom		£8,158
		CC	**Costs**	£58,048[g]			-£2,240		-£32,029		-£21,776[e]		£15,648	£529	-£2,595		£22,687
			QALYs	9.71			0.59		0.13		0.10[e]		4.16	1.11	1.21		4.78
			iCER				Dom		Dom		Dom[e]		£3,762	£477	Dom		£4,746
GT2	**TN**	**non-CC**	**Costs**	[redacted]									**£20,729**			-£8,665[e]	£16,210
			QALYs										**0.63**			0.11[e]	3.12
			iCER										**£32,903**			Dom[e]	£5,196
		CC	**Costs**	[redacted]									£18,094			-£9,375[e]	£12,619
			QALYs										1.46			0.35[e]	5.20
			iCER										£12,393			Dom[e]	£2,427
	TE	**non-CC**	**Costs**	[redacted]									£11,378			-£10,595	£16,394
			QALYs										1.82			0.53	2.77
			iCER										£6,252			Dom	£5,918
		CC	**Costs**	[redacted]									£7,740			-£8,154	£11,490
			QALYs										3.00			-0.01	4.83
			iCER										£2,580			£1.6 mil	£2,379

				Totals	Increments versus SOF/VEL (12w)[b]											
					Regimens not containing RBV/P			Regimens containing RBV/P								BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT3	**TN**	**non-CC**	**Costs**	£42,190[g]		-£23,951[e]							**£29,872**				£23,504
			QALYs	17.24		0.90[e]							**1.24**				4.41
			iCER			Dom[e]							**£24,090**				£5,330
		CC	**Costs**	£60,724[g]							-£27,470[e]		£23,526		£997	-£36,505[e]	£24,934
			QALYs	9.82							1.82[e]		3.24		0.11	0.97[e]	4.84
			iCER								Dom[e]		£7,261		£9,064	Dom[e]	£5,152
	TE	**non-CC**	**Costs**	£42,705[g]		-£23,833[e]							£21,470		£2,180		£25,058
			QALYs	15.98		0.78[e]							2.21		-0.08		3.61
			iCER			Dom[e]							£9,715		Dom		£6,941
		CC	**Costs**	£59,792[g]							-£24,859[e]		£20,681		£1,058	-£38,604[e]	£24,431
			QALYs	9.26							0.97[e]		2.50		0.19	1.47[e]	4.33
			iCER								Dom[e]		£8,272		£5,568	Dom[e]	£5,642
GT4	**TN**	**non-CC**	**Costs**	£41,862[g]		-£20,521[e]		**£5,670**	**£12,149**				£21,352	£8,416			£25,906
			QALYs	17.32		0.00[e]		**0.01**	**0.22**				2.00	0.62			3.57
			iCER			Dom[e]		**£567,000**	**£55,223**				£10,676	£13,574			£7,257
		CC	**Costs**	£59,524[g]			**£588**	-£32,602	-£825	-£25,127[e]			£16,182	£4,771	-£7,309		£23,734
			QALYs	10.18			**0.00**	0.34	0.30	1.89[e]			3.75	1.71	2.60		5.20
			iCER				**Dom**	Dom	Dom	Dom[e]			£4,315	£2,790	Dom		£4,564
	TE	**non-CC**	**Costs**	£41,226[g]		-£20,521	-£1,577	**£5,670**	-£665				£21,884	£362			£26,228
			QALYs	16.32		0.00	0.48	**0.01**	0.15				1.76	1.23			3.14
			iCER			Dom	Dom	**£567,000**	Dom				£12,434	£294			£8,353
		CC	**Costs**	£57,892[g]			**£597**	-£32,185	-£21,431	-£26,759[e]			£15,915	-£4,481	-£7,494		£22,531
			QALYs	9.78			**0.00**	0.20	1.02	1.49[e]			3.49	2.47	2.43		4.85
			iCER				**Dom**	Dom	Dom	Dom[e]			£4,560	Dom	Dom		£4,646
GT5	**TN**	**non-CC**	**Costs**	[redacted]									£10,958				£15,512
			QALYs										1.88				3.45
			iCER										£5,829				£4,496

				Totals	Increments versus SOF/VEL (12w)[b]											
					Regimens not containing RBV/P			Regimens containing RBV/P								BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT6	**TN**	**non-CC**	**Costs**	[redacted]									£10,438				£14,992
			QALYs										2.00				3.57
			iCER										£5,219				£4,199
GT5/6[f]	**TN**	**CC**	**Costs**	[redacted]									£5,268		-£18,223		£12,820
			QALYs										3.75		2.60		5.20
			iCER										£1,405		Dom		£2,465
	TE	**non-CC**	**Costs**	[redacted]									£10,969				£15,313
			QALYs										1.76				3.14
			iCER										£6,232				£4,877
		CC	**Costs**	[redacted]									£5,001		-£18,408		£11,617
			QALYs										3.49		2.43		4.85
			iCER										£1,433		Dom		£2,395
DCC	**TN**		**Costs**	[redacted]								-£7,329					
			QALYs									0.16					
			iCER									Dom					
	TE		**Costs**	[redacted]								-£7,493					
			QALYs									0.15					
			iCER									Dom					

Abbreviations: TN, treatment naïve; TE, treatment experienced; Dom, dominance; iCER, incremental cost-effectiveness ratio;
[a]To be consistent with the results presented in the CS, the incremental costs, QALYs and ICERs were recalculated by the ERG from the results presented in the CS. As a result, rounding errors might be induced. In addition, after consulting a clinical expert it was decided not to present the results for GT1a and GT1b but to present the results for the combined GT1 group only. This was done as it is consistent with the final scope and for reading convenience, given the amount of subgroups and comparators considered. Although there is some evidence of a differential response for GT1a and GT1b, this difference is small in magnitude and is unlikely to be a major issue from a clinical perspective.
[b]For DCC this is SOF/VEL/RBV. [c]Retrieved from GT1b subgroup. [d]Retrieved from GT1a subgroup. [e]Only presented by the company in the analysis for IFN ineligible patients.
[f]The results for GT5 and GT6 were in part combined since these were identical. [g]Based on (anticipated) list price for SOF/VEL.

5.2.10 Sensitivity analyses

Both probabilistic sensitivity analyses and deterministic sensitivity analyses were performed by the company.

Probabilistic sensitivity analyses

Probabilistic sensitivity analyses were provided by the company in Tables 177-218 and Figures 18-59. This is summarised by the ERG in Table 5.18. The probability that SOF/VEL is cost effective ranged between 18%-93% for a threshold value of £20,000 and between 23%-95% for a threshold value of £30,000.

Table 5.18: Company PSA results; probability that SOF/VEL is cost effective[a]

			Price SOF/VEL	Threshold: £20,000	Threshold: £30,000
GT1	**TN**	**non-CC**	Anticipated list price	18%	23%
		CC	Anticipated list price	45%	44%
	TE	**non-CC**	Anticipated list price	40%	38%
		CC	Anticipated list price	53%	50%
GT2	**TN**	**non-CC**	Discounted price	42%	54%
		CC	Discounted price	61%	67%
	TE	**non-CC**	Discounted price	87%	83%
		CC	Discounted price	64%	61%
GT3	**TN**	**non-CC**	Discounted price	59%	71%
		CC	Discounted price	63%	59%
	TE	**non-CC**	Discounted price	64%	57%
		CC	Discounted price	65%	63%
GT4	**TN**	**non-CC**	Anticipated list price	41%	48%
		CC	Discounted price	58%	55%
	TE	**non-CC**	Anticipated list price	34%	39%
		CC	Discounted price	56%	52%
GT5	**TN**	**non-CC**	Discounted price	91%	94%
		CC	Discounted price	91%	90%
	TE	**non-CC**	Discounted price	87%	92%
		CC	Discounted price	89%	88%
GT6	**TN**	**non-CC**	Discounted price	93%	95%
		CC	Discounted price	87%	87%
	TE	**non-CC**	Discounted price	90%	93%
		CC	Discounted price	90%	90%
DCC	**TN**		Discounted price	78%	79%
	TE		Discounted price	77%	78%

[a]For DCC this is SOF/VEL/RBV

ERG comment: The model only allows comparison of SOF/VEL with one other comparator simultaneously. As a result, the multiple comparators, which are considered consecutively in the probabilistic sensitivity analyses, are based on different 'random seeds', which is methodologically incorrect. Therefore, the probabilistic sensitivity analyses results presented by the company are potentially biased and make it difficult to interpret them. Moreover, as not all relevant comparators

identified in the final scope are incorporated in the base-case (see Table 5.16) and hence in the probabilistic sensitivity analyses, the probabilities of being cost effective presented in Table 5.18 might be overestimated.

Deterministic sensitivity analyses
In order to examine the uncertainty of the results, one-way deterministic sensitivity analyses were performed by the company. In these analyses, the input parameters are varied one at a time to show the impact of each parameter on the model results. See Table 219 and 220 of the CS for the values used for the input parameters in these analyses.

The results of the one-way deterministic sensitivity analyses are presented using tornado diagrams and Tables (see Figures 60-63 and Tables 221-224). Only the results of the one-way deterministic sensitivity for the treatment-naïve non-cirrhotic subgroups for GT1-GT4 are presented.

These selected subset of one-way deterministic sensitivity analyses showed that the model results (i.e. ICER) are most sensitive (ICER range >£10,000) to the following parameters:

- Treatment costs (for ledipasvir/sofosbuvir and sofosbuvir/velpatasvir);
- Discount rates (costs and outcomes);
- SVR probability (for Ledipasvir/sofosbuvir, Peg-IFN+RBV and Sofosbuvir/velpatasvir);
- Utility non cirrhotic (baseline).

ERG comment: Given the large volume of subgroups and comparators considered in this assessment, the ERG will only present a subset of the deterministic sensitivity analyses in section 5.8.2 of the CS. However, the ERG would prefer to present a complete overview of deterministic sensitivity analyses in an appendix, which was unfortunately not done by the company. Moreover, if a subset is presented, it is, according to the ERG, essential to present an overview representative for all deterministic sensitivity analyses, including all subgroups. Given that the company only provide deterministic sensitivity analyses for treatment-naïve non-cirrhotic subgroups, it is questionable whether these analyses provide a good reflection of the parameters that have the largest impact on the model results.

5.2.11 Model validation and face validity check

Transparency
The company's cost effectiveness model was developed in Excel and contained multiple hidden worksheets, columns and rows and cells with a white background containing white text, which were not visible.

Internal validity
The CS reported that a health economist performed internal validation in three steps. *"Firstly, the model was assessed using the Phillips et al, (2004) checklist.*[99] *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"*[1]

External validity
External validation was performed as follows: "*KOL input was sought to validate major assumptions in the SOF/VEL model. An external health economist undertook a comprehensive validation of the assumptions and results of the model.*"[1]

Cross-validity
No cross validation was performed.

ERG comment:

Transparency
To be able to assess the Excel model, the ERG requested the company to provide a model without hidden worksheets, columns and rows, and to make all cell inputs visible. The company refused to fulfil this request because these hidden elements were meant to increase the user-friendliness and transparency of the model.[28] The ERG disagrees that hiding elements of the model increases the transparency of the model.

In addition, the implementation of the cohort simulation in the Excel model was not transparent. The simulation contained multiple 'IF'-functions and the simulation was different in the first 37 cycles of the simulation (cycle 0 included). This hampered the ERG in reproducing the cohort simulation and in performing additional analyses.

Internal validation
The different internal validation steps undertaken by the company seem appropriate. However, the results of these efforts were not provided and the ERG discovered three mistakes in the cost effectiveness model.

Firstly, the 'check' in the cohort simulation (column BH in the 'Model patient'-tab) is not reliable as from cycle eight not all patients are selected. This error indicates that patients are counted twice in different health states of the cohort simulation (i.e. the health states 'Post-liver transplant', 'Post-liver transplant (Yr1)' and 'Post-liver transplant (Yr2)'). Secondly, for the first 38 cycles (including cycle 0), the company calculates transition probabilities and time in the model based on a year consisting of 48 weeks (the cycle of two weeks was assumed to equal 1/24 year). After 38 cycles the model has not run for two years, as the company states, but 98 weeks. Furthermore, the tunnel state for liver transplant is not adjusted for the shorter cycle lengths. As a consequence, the impact of a liver transplant on QALY (utility and mortality risk) and costs is underestimated for liver transplants that occur during the first 38 cycles (98 weeks) in the model.

External validation
The company did not provide details (e.g. which questions were asked to the experts, which external sources were used) about how the model was externally validated by experts in their submission. Details were still not provided after request from the ERG. Lack of transparency on external validation of model outcomes is a violation of good modelling practices.[100]

Cross validation

Because of the lack of cross validation in the CS, the ERG asked the company to validate model outcomes against previous assessments. The company refused to provide the requested cross validation (clarification question C17[48]). Only one cross validation of the economic results of LDV/SOF between the current assessment and the results from the ERG report of TA363 was provided.[101] The company concluded that *"both costs and QALYs were very similar for LDV/SOF (12 weeks)."* (response to the clarification letter, Table 41).[28] The ERG agrees that the presented results are similar, but the lack of extensive cross validation of the model is a violation of good modelling practices.[100] Consequently, the ERG performed a limited (due to time constraints) cross validation of the model outcomes (costs and QALY estimates for PR and SMV/PR) for GT1 TN patients based on the outcomes from TA331[14], Westerhout et al., 2015[51] (provided in the clarification response,[28]) and the ERG report of TA363[101] (Table 5.19). These treatments were chosen pragmatically because they were represented for the same subpopulation in different assessments. This cross validation showed that the results in the CC population are lower in the current assessment than in the TA363 ERG report, most profoundly for SMV/PR. The results for the non-CC population in the current assessment are in the range of outcomes reported in the other sources. It is not possible to draw general conclusions from this cross validation, but it does highlight the importance of thorough cross validation, and the explanation of identified discrepancies in company submissions.

Table 5.19: Cross validation of model outcomes for GT1 TN patients.

Treatment	Cirrhotic status	Outcomes	Current assessment	TA363[1]	TA331[2]	Westerhout et al.[2]
PR (24/48w)	non-CC	QALY	[redacted]	15.96	11.65	11.65
		Costs	[redacted]	£19,205	£26,316	£25,358
	CC	QALY	[redacted]	6.54		
		Costs	[redacted]	£48,266		
SMV/PR	non-CC	QALY	[redacted]	17.09	11.26	12.78
		Costs	[redacted]	£61,416	£43,544	£36,298
	CC	QALY	[redacted]	9.88		
		Costs	[redacted]	£81,485		

[1]As reported in Table 52 of ERG report of TA363 (ERG preferred base-case)
[2]As reported in response to clarification letter[28]
PR= pegylated-interferon alfa in combination with ribavirin; SMV/PR= simeprevir in combination with pegylated-interferon alfa and ribavirin; Non-CC=non-cirrhotic; CC=cirrhotic

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations from section 5.2, the ERG defined a new base-case (see Table 6.1). This base-case included multiple adjustments to the original base-case presented in the CS (see Appendix 4 for the adjustments made in the model). These adjustments were subdivided into three categories (derived from Kaltenthaler et al., 2016[102]):

1. Fixing errors (correcting the model were the company's submitted model was unequivocally wrong);
2. Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to);
3. Matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred).

The combination of these corrections/amendments resulted in the ERG base-case (Table 6.1).

Fixing errors

1. Correcting the transition probabilities (based on the literature) calculated by the company (see section 5.2.6)

Fixing violations

2. Incorporating an annual reinfection probability of 2.4% for the non-cirrhotic and (de)compensated cirrhosis states (see section 5.2.2)

Matters of judgment

3. Not applying the SVR utility increment for decompensated cirrhosis (see section 5.2.8)

Although the ERG defined a new base-case, not all issues raised by the ERG could be quantified and included in the ERG base-case. This include the following issues:

- Arbitrary selection and single arm comparisons of SVR rates (one of the main drivers of the model);
- Lack of face/internal validity of the model (e.g. assuming a year with 48 weeks, incorporating a period without any disease progression and mortality, not adjusting the liver transplant tunnel for shorter cycle lengths, not incorporating effects on the population infection rate);
- Simplifications in the model structure (i.e. not distinguishing between mild and moderate cirrhosis);
- Not systematically selecting all transition probabilities in the model;
- Not using the HRQOL evidence collected in the ASTRAL trials;
- Not providing sufficient justifications for (sources used for) the on-treatment utility increments.

Particularly the use of single arm studies for SVR rates should be regarded as a severe limitation as this raises the question whether the differences in SVR rates between the comparators are true differences between the comparators or whether these differences are driven by differences between the studies used to obtain SVR rates (e.g. difference in study population, context, design). Therefore, any analyses (both by the company and ERG) should be interpreted with extreme caution. Additionally, it should be noted that not all comparators were included in the model received by the ERG (see Table 6.1 for more details), hence the ERG could not calculate the results for these comparators or was forced to make assumptions for this purpose (e.g. assuming the results for DCV/SOF/RBV are equal to DCV/SOF for GT1 (CC)). In particular the inability to calculate results for DCV/PR was considered an issue by the ERG as this resulted in an ICER larger than £30,000 in the company's analysis compared with SOF/VEL (see Table 5.17).

Given the large volume of analyses and results in this assessment, the results of the abovementioned corrections/amendments are not presented separately. Only the combined ERG base-case is presented (see Table 6.1). Moreover, the ERG did not perform probabilistic analyses because the economic model submitted by the company was unable to consider multiple comparators simultaneously in the probabilistic analyses (see section 5.2.10 for more details).

In the ERG base-case (Table 6.1), SOF/VEL was more effective (in terms of QALYs) than the other compactors, exceptions being in all subgroups with 3D and some of the subgroups with DCV/SOF (12w) and SOF/PR (12w). Additionally, SOF/VEL is more expensive than 3D, 2D/RBV (12/24w), PR (24/48w), SMV/PR and BSC while SOF/VEL is less expensive than DCV/SOF (12w) and SOF/RBV (12/24w). For the other comparisons this was dependent on the subgroup considered.

For a willingness to pay of £20,000 and £30,000 per QALY, SOF/VEL was in general cost effective compared to most comparators. However, based on a willingness to pay of £20,000 and £30,000, SOF/VEL (anticipated list price) was not cost effective compared to:

- 3D (GT1 TN and TE non-cirrhotic);
- LDV/SOF (GT1 TN non-cirrhotic, GT4 TN and TE cirrhotic);
- 2D/RBV (GT4 TN and TE non-cirrhotic);
- 3D/RBV (GT1 TN and TE non-cirrhotic);
- PR (GT3 TN non-cirrhotic) and;
- SOF/PR (GT3 TE non-cirrhotic).

It should be noted that in the company's base-case SOF-VEL was not cost effective compared with DCV/PR (GT4 TN non-cirrhotic), however as mentioned above, the results for this comparator could not be calculated by the ERG. Moreover, based on a willingness to pay of £20,000 and £30,000, SOF/VEL (discounted price) was not cost effective compared to PR (GT2 TN non-cirrhotic).

5.4 Conclusions of the cost effectiveness section

The economic model described in the CS is considered by the ERG to meet the NICE reference case and is in line with the decision problem specified in the scope.

The model structure is conceptually similar to the models that were submitted in previous assessments of HCV treatment. According to the ERG the model structure reasonably reflects the key elements of HCV disease, although some simplifications were made. Not including reinfection in the model structure favours all active treatments. According to the ERG a structure that allows for re-infection is more in line with clinical practice and will hence be used in the ERG additional analyses.

Single arms from RCTs were used to estimate model inputs for SVR, discontinuation and AE rates for SOF/VEL and its comparators. The ERG has concerns about the validity of this naïve comparison of single study arms, which is not in line with the evidence synthesis best practices and susceptible to bias. It raises the question whether the differences in SVR rates between the comparators are true differences between the comparators or whether these differences are driven by differences between the studies used to obtain SVR rates (e.g. difference in study population, context, design). Therefore, any analysis (both from the company and ERG) should be interpreted with extreme caution.

Other disease progression related transition probabilities were not dependent on the treatment or GT status, and taken from literature sources. The ERG considered the targeted search to identify these

sources as inadequate. In addition, the ERG discovered calculation errors in these probabilities, which were corrected in the ERG additional analyses.

SF-6D utilities from the ASTRAL trials could have been used by the company in their cost effectiveness analysis instead of the utilities from the literature. The ERG has concerns about the estimates of on-treatment utility increments and decrements. In addition, the ERG questioned the use of a SVR utility increment for the decompensated cirrhosis health state. This utility increment was removed in the ERG additional analyses.

The ERG thinks that the cost effectiveness analysis based on list prices may not reflect the actual value for money of the HCV treatments.

The ERG has concerns about the validation status of the cost effectiveness analysis. The Excel model suffered from a lack of transparency and mistakes were detected in the technical implementation of the model. No details were given concerning the external validation and cross validation was completely lacking.

Not all issues raised by the ERG could be quantified and included in the ERG base-case. This includes the following:

- Arbitrary selection and single arm comparisons of SVR rates (one of the main drivers of the model);
- Lack of face / internal validity of the model (e.g. assuming a year with 48 weeks, incorporating a period without any disease progression and mortality, not adjusting the liver transplant tunnel for shorter cycle lengths, not incorporating effects on the population infection rate);
- Simplifications in the model structure (i.e. not distinguishing between mild and moderate cirrhosis);
- Not systematically identifying sources for all transition probabilities in the model;
- Not using the HRQOL evidence collected in the ASTRAL trials;
- Not providing sufficient justifications for (sources used for) the on-treatment utility increments.

Additionally, it should be noted that not all comparators were included in the model provided by the company (see Table 6.1 for more details), hence the ERG could not calculate the results for these comparators or was forced to make assumptions for this purpose (e.g. assuming the results for DCV/SOF/RBV are equal to DCV/SOF for GT1 (CC)). In particular, the inability to calculate results for DCV/PR was considered an issue, as this resulted in an ICER of £55,223 for the company's base-case compared with SOF/VEL (see Table 5.17).

The ERG created a new base-case by correcting calculation errors in transition probabilities, incorporating reinfection, and removing the SVR utility increment for the decompensated cirrhosis health state. Given the large volume of analyses and results in this assessment, the results of the ERG's adaptations are not presented separately. Only the combined ERG base-case is presented (see Table 6.1). Also, the ERG did not perform probabilistic analyses because the economic model submitted by the company was unable to consider multiple comparators simultaneously in the probabilistic analyses (see section 5.2.10 for more details). For a willingness to pay of £20,000 and £30,000, in the ERG base case SOF/VEL (anticipated list price) was not cost effective compared to:

- 3D (GT1 TN and TE non-cirrhotic);
- LDV/SOF (GT1 TN non-cirrhotic, GT4 TN and TE cirrhotic);
- 2D/RBV (GT4 TN and TE non-cirrhotic);
- 3D/RBV (GT1 TN and TE non-cirrhotic);
- PR (GT3 TN non-cirrhotic) and;
- SOF/PR (GT3 TE non-cirrhotic).

These results are similar to the CS base-case, as SOF/VEL is not cost effective in comparison to the same comparators (only SOF/PR in GT3 treatment experienced non-cirrhotic patients was added). As mentioned above, for DCV/PR (GT4 TN non-cirrhotic), no results could be calculated by the ERG. SOF/VEL (discounted price) was not cost effective compared to PR (GT2 TN non-cirrhotic). However, the results of these additional analyses by the ERG should be interpreted with caution, as they were based on treatment effectiveness parameters that were based on questionable assumptions/methods.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Table 6.1: ERG base-case results (discounted price for SOF/VEL unless stated otherwise)

				Totals	Increments versus SOF/VEL (12w)[b]												
					Regimens not containing RBV/P			Regimens containing RBV/P									BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT1	**TN**	**non-CC**	**Costs**	£46,568[g]	**£4,471**	-£20,447	**£12,472**		**£2,969**				£23,643	£8,980	£978		£30,096
			QALYs	16.375	**-0.018**	-0.045	**0.131**		**0.053**				1.542	0.499	0.222		2.760
			iCER		**Dom**	£458,950	**£95,563**		**£56,005**				£15,334	£18,000	£4,405		£10,904
		CC	**Costs**	£64,906[g]			-£449		-£32,119		-£20,445[e]		£19,966	£5,831	-£430		£28,926
			QALYs	8.971			0.172		0.175		-0.057[e]		2.795	1.461	0.718		3.891
			iCER				Dom		Dom		£356,954[e]		£7,144	£3,991	Dom		£7,433
	TE	**non-CC**	**Costs**	£45,343[g]	**£4,047**	-£20,453	-£418		**£2,841**				£23,114	£3,675	-£862		£29,858
			QALYs	15.539	**-0.04**	-0.040	0.074		**0.075**				2.017	0.513	0.641		2.475
			iCER		**Dom**	£512,536	Dom		**£37,895**				£11,462	£7,157	Dom		£12,063
		CC	**Costs**	£63,139[g]			-£1,632		-£31,825		-£20,629[e]		£20,091	£1,844	-£1,368		£27,611
			QALYs	8.716			0.449		0.072		0.002[e]		3.177	0.802	0.931		3.688
			iCER				Dom		Dom		Dom[e]		£6,325	£2,299	Dom		£7,487
GT2	**TN**	**non-CC**	**Costs**	[redacted]									**£21,517**			-£8,538[e]	£20,194
			QALYs										**0.483**			0.088[e]	2.367
			iCER										**£44,545**			Dom[e]	£8,532
		CC	**Costs**	[redacted]									£19,585			-£9,033[e]	£17,736
			QALYs										1.091			0.269[e]	3.949
			iCER										£17,947			Dom[e]	£4,492
	TE	**non-CC**	**Costs**	[redacted]									£13,697			-£9,950	£19,894
			QALYs										1.398			0.409	2.136
			iCER										£9,798			Dom	£9,312

				Totals	Increments versus SOF/VEL (12w)[b]											
					Regimens not containing RBV/P			Regimens containing RBV/P								BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
		CC	**Costs**	[redacted]									£11,017			-£8,175	£16,467
			QALYs										2.273			0.000	3.727
			iCER										£4,846			Dom	£4,419
GT3	**TN**	**non-CC**	**Costs**	£47,476[g]		-£22,907[e]							**£31,297**				£28,527
			QALYs	16.158		0.691[e]							**0.949**				3.369
			iCER			Dom[e]							**£32,981**				£8,467
		CC	**Costs**	£65,673[g]							-£25,672[e]		£26,781		£1,085	-£35,462[e]	£29,694
			QALYs	8.757							1.379[e]		2.440		0.093	0.717[e]	3.677
			iCER								Dom[e]		£10,975		£11,662	Dom[e]	£8,076
	TE	**non-CC**	**Costs**	£47,029[g]		-£22,949[e]							£24,049		**£2,043**		£29,137
			QALYs	15.149		0.601[e]							1.707		**-0.057**		2.813
			iCER			Dom[e]							£14,088		**Dom**		£10,357
		CC	**Costs**	£64,416[g]							-£23,862[e]		£23,438		£1,231	-£37,009[e]	£28,888
			QALYs	8.372							0.744[e]		1.890		0.154	1.111[e]	3.343
			iCER								Dom[e]		£12,401		£7,982	Dom[e]	£8,640
GT4	**TN**	**non-CC**	**Costs**	£46,388[g]	[h]			**£5,670**	[h]				£23,838	[h]			£30,275
			QALYs	16.448	[h]			**0.014**	[h]				1.510	[h]			2.715
			iCER		[h]			**£393,002**	[h]				£15,783	[h]			£11,150
		CC	**Costs**	£64,830[g]			**£588**	£27,882	[h]		[h]		£20,057	[h]	-£4,749		£28,851
			QALYs	9.029			**0.000**	3.949	[h]		[h]		2.800	[h]	1.974		3.949
			iCER				**Dom**	£7,060	[h]		[h]		£7,162	[h]	Dom		£7,306
	TE	**non-CC**	**Costs**	£45,182[g]	[h]		-£990	**£5,670**	[h]				£24,059	[h]			£30,043
			QALYs	15.602	[h]		0.370	**0.014**	[h]				1.357	[h]			2.435
			iCER		[h]		Dom	**£393,002**	[h]				£17,734	[h]			£12,337
		CC	**Costs**	£63,057[g]			**£597**	£27,392	[h]		[h]		£19,702	[h]	-£4,993		£27,529
			QALYs	8.771			**0.000**	3.743	[h]		[h]		2.647	[h]	1.870		3.742
			iCER				**Dom**	£7,318	[h]		[h]		£7,442	[h]	Dom		£7,356

				Totals	Increments versus SOF/VEL (12w)[b]											
					Regimens not containing RBV/P			Regimens containing RBV/P								BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT5	**TN**	**non-CC**	**Costs**	[redacted]									£13,293				£19,730
			QALYs										1.418				2.623
			iCER										£9,376				£7,523
GT6	**TN**	**non-CC**	**Costs**	[redacted]									£12,923				£19,361
			QALYs										1.510				2.715
			iCER										£8,557				£7,130
GT5/6[f]	**TN**	**CC**	**Costs**	[redacted]									£9,142		-£15,664		£17,937
			QALYs										2.800		1.974		3.949
			iCER										£3,265		Dom		£4,542
	TE	**non-CC**	**Costs**	[redacted]									£13,145				£19,129
			QALYs										1.357				2.435
			iCER										£9,689				£7,855
		CC	**Costs**	[redacted]									£8,788		-£15,908		£16,615
			QALYs										2.647		1.870		3.742
			iCER										£3,319		Dom		£4,440
DCC	**TN**		**Costs**	[redacted]								-£7,721					
			QALYs									0.129					
			iCER									Dom					
	TE		**Costs**	[redacted]								-£7,852					
			QALYs									0.122					
			iCER									Dom					

Abbreviations: TN, treatment naïve; TE, treatment experienced; Dom, dominance; iCER, incremental cost-effectiveness ratio;

[a]After consulting a clinical expert it was decided not to present the results for GT1a and GT1b but to present the results for the combined GT1 group only. This was done as it is consistent with the final scope and for reading convenience, given the amount of subgroups and comparators considered. Although there is some evidence of a differential response for GT1a and GT1b, this difference is small in magnitude and is unlikely to be a major issue from a clinical perspective.

	Totals	Increments versus SOF/VEL (12w)[b]											
		Regimens not containing RBV/P			Regimens containing RBV/P								BSC
	SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC

[b]For DCC this is SOF/VEL/RBV
[c]Retrieved from GT1b subgroup
[d]Retrieved from GT1a subgroup
[e]Only presented by the company in the analysis for IFN ineligible patients. Additionally, as the DCV/SOF/RBV comparator was not included for GT1 (CC) in the model received by the ERG, the ERG used DCV/SOF (12w) as a proxy for this comparator.
[f]The results for GT5 and GT6 were in part combined since these were identical.
[g]Based on (anticipated) list price for SOF/VEL
[h]This comparator was not included (for this specific subgroup) in the model received by the ERG and hence no results could be presented for the ERG base-case.

7. OVERALL CONCLUSIONS

7.1 Statement of principal findings

The conclusion from the SOF/VEL trials is that SOF/VEL has high SVR rates in all genotypes. In addition, SOF/VEL has a relative favourable safety and tolerability profile. Generally, the three SOF/VEL trials were well conducted. However, ASTRAL-3 and 2 were open-label studies; therefore, care providers, participants and outcome assessors were not blinded to treatment allocation. In addition, in ASTRAL-3 there was a greater number of dropouts in the SOF/RBV treatment arm than in the intervention arm (n=21, vs. n=2 in SOF/VEL arm). Both issues mean that these trials are at a higher risk of bias.

The main concern regarding clinical effectiveness is that comparator data (for SVR12 and AEs) were taken from single arms of randomised controlled trials (RCTs). Overall, the justifications provided by the company for each selected SVR rate seem valid. However, it would be quite easy to provide an equally valid justification for most of the alternative sources. Therefore, the main problem with this method of selecting inputs for the economic model still stands: using only one source for each intervention and population increases the chance of bias and cherry-picking.

The economic model described in the CS is considered by the ERG to meet the NICE reference case and is in line with the decision problem specified in the scope. The economic model structure reflects the main aspects of chronic HCV disease. The ERG raised a number of issues. Not all issues of these issues could be quantified and included in the ERG base-case. This includes the following:

- Arbitrary selection and single arm comparisons of SVR rates (one of the main drivers of the model);
- Lack of face / internal validity of the model (e.g. assuming a year with 48 weeks, incorporating a period without any disease progression and mortality, not adjusting the liver transplant tunnel for shorter cycle lengths, not incorporating effects on the population infection rate);
- Simplifications in the model structure (i.e. not distinguishing between mild and moderate cirrhosis);
- Not systematically identifying sources for all transition probabilities in the model;
- Not using the HRQOL evidence collected in the ASTRAL trials;
- Not providing sufficient justifications for (sources used for) the on-treatment utility increments.

The ERG mainly has concerns about the validity of this naïve comparison of single study arms, which is not in line with the evidence synthesis best practices and susceptible to bias. It raises the question whether the differences in SVR rates between the comparators are true differences between the comparators or whether these differences are driven by differences between the studies used to obtain SVR rates (e.g. difference in study population, context, design). Therefore, any analysis (both from the company and ERG) should be interpreted with extreme caution.

It should be noted that not all comparators were included in the model provided by the company (see Table 6.1 for more details), hence the ERG could not calculate the results for these comparators or was forced to make assumptions for this purpose (e.g. assuming the results for DCV/SOF/RBV are equal to DCV/SOF for GT1 (CC)). In particular the inability to calculate results for DCV/PR was

considered an issue, as this resulted in an ICER larger than £30,000 in the company's analysis compared with SOF/VEL (see Table 5.17).

The ERG created a new base-case by correcting calculation errors in transition probabilities, incorporating reinfection, and removing the SVR utility increment for the decompensated cirrhosis health state. For a willingness to pay of £20,000 and £30,000, in the ERG base case SOF/VEL (anticipated list price) was not cost effective compared to:

- 3D (GT1 TN and TE non-cirrhotic);
- LDV/SOF (GT1 TN non-cirrhotic, GT4 TN and TE cirrhotic);
- 2D/RBV (GT4 TN and TE non-cirrhotic);
- 3D/RBV (GT1 TN and TE non-cirrhotic);
- PR (GT3 TN non-cirrhotic) and;
- SOF/PR (GT3 TE non-cirrhotic).

These results are similar to the CS base-case, as SOF/VEL is not cost effective in comparison to the same comparators (only SOF/PR in GT3 treatment experienced non-cirrhotic patients was added). As mentioned above, for DCV/PR (GT4 TN non-cirrhotic), no results could be calculated by the ERG. SOF/VEL (discounted price) was not cost effective compared to PR (GT2 TN non-cirrhotic). However, the results of these additional analyses by the ERG should be interpreted with caution, as they were based on treatment effectiveness parameters that were based on questionable assumptions/methods.

7.2 Strengths and limitations of the assessment

The company's submitted evidence on clinical effectiveness broadly covered the final scope set out by NICE. The review of SOF/VEL trials included all relevant trials in which SOF/VEL had been used. Reviews for other treatments were likely to have identified the majority of trials of other relevant treatments. The submission covers the key clinical outcomes, including SVR rates, adverse events and mortality.

The economic model structure reflects the main aspects of the chronic HCV disease, meets the NICE reference case to a large extent and is mostly in line with the decision problem specified in the scope.

Clinical effectiveness searches were limited by date from 2006, however a key trial published in 2004 (Zeuzem et al., 2004[26]) was included in the NMA. It was unclear how this study was found. Searches were not conducted to identify non-RCT evidence.

The main concern regarding clinical effectiveness is that comparator data (for SVR12 and AEs) were taken from single arms of randomised controlled trials (RCTs). Overall, the justifications provided by the company for each selected SVR rate seem valid. However, it would be quite easy to provide an equally valid justification for most of the alternative sources. Therefore, the main problem with this method of selecting inputs for the economic model still stands: using only one source for each intervention and population increases the chance of bias and cherry-picking.

The cost effectiveness analyses were based on the treatment effectiveness data and all health economic analyses thus suffered from the uncertainty of evidence synthesis as well. Furthermore, some analyses were conducted on list prices, which may not reflect the actual value for money of the treatments.

The ERG has concerns regarding the validation status of the cost effectiveness analysis. The Excel model suffered from a lack of transparency and mistakes were detected in the technical implementation of the model. No details were given concerning the external validation and cross validation was completely lacking.

7.3 Suggested research priorities

Head to head trials of direct-acting antivirals (DAAs) are warranted in patients with HCV.

Data for certain subgroups, such as patients who underwent a liver transplant, is scarce. Re-analysis of data and data collection in this clinical subgroups is warranted.

In the current landscape, a MTA of non-DAA, partly DAA and all-DAA treatment regimens and treatment sequences, would guide the decision makers and benefit the efficient use of resources of the UK healthcare system.

Also, recently, it was advocated in the literature that lower cost effectiveness thresholds should be considered for new chronic HCV treatments, given the potential large financial burden on the health system of reimbursing these drugs.[103] If this opinion is shared among the decision makers, methods to determine this threshold would be needed.

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Appendix 1: Further critique of searches in the company submission

Clinical effectiveness

- The ERG noted inclusion of search phrases with incorrect punctuation* for some of the comparators, which the Ovid interface was unable to process correctly; e.g. (from line 4 of the Medline strategy):

  "N-(3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl)-3-(2-((((1,1-dimethylethyl)amino)carbonyl)amino)-3,3-dimethyl-1-oxobutyl)-6,6-dimethyl-3-azabicyclo(3.1.0)hexan-2-carboxamide").

*Terms such as this were also included in the Cochrane Library and both Embase searches.

- The Embase search strategies did not include an appropriate Emtree indexing term (*"hepatitis C, chronic"/*). When the ERG queried this omission, the clarification response explained that as the Emtree term was newly introduced on Embase (date of introduction: 1.5.15), the risk of missing studies was "minimal". The ERG concluded inclusion of this term would have benefited recall of the company's clinical effectiveness search in Embase.

Appendix 2: ERG search strategy

Health Technology Assessment (HTA) database (via Wiley): Issue 2 – April 2016
NHS Economic Evaluation Database (NHS EED) (via Wiley): Issue 2 – April 2015
Searched 14.7.16

#1 [mh "hepatitis c"] 2525
#2 "hepatitis c" or hcv or "hep c" 6523
#3 #1 or #2 6523
#4 [mh "health economics"] or [mh "economic evaluation"] or [mh "cost-benefit analysis"] or [mh "cost effectiveness analysis"] or [mh "cost minimization analysis"] or [mh "cost utility analysis"] 24614
#5 cost* near/2 (effective* or utility* or benefit* or minimi* or consequence*) 35827
#6 (economic* or pharmacoeconomic*) near/2 (evaluat* or model* or analys?s) 23522
#7 ("quality adjusted life year*" or qaly* or "life year* gained" or "life year* equivalent*" or "incremental cost effective*" or icer) 9515
#8 #4 or #5 or #6 or #7 42923
#9 #3 and #8 499
#10 [mh sofosbuvir] or sofosbuvir or sovaldi* or hepcinat* or hepcvir* or sovihep* or harvoni* 196
#11 boceprevir or victrelis* 184
#12 daclatasvir or daklinza* 74
#13 danoprevir 46
#14 dasabuvir or exviera* 46
#15 elbasvir 16
#16 Grazoprevir or zepatier* 17
#17 ledipasvir 64
#18 ombitasvir or viekirax* or paritaprevir or veruprevir or "viekira pak*" or technivie* 52
#19 [mh simeprevir] or simeprevir or olysio* or galexos* or sovriad* 86
#20 telaprevir or incivo* or incivek* or telavic* 253
#21 velpatasvir 10
#22 "direct acting antiviral*" or DAA* 443
#23 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 1071
#24 #9 and #23 52
#25 #24 in Technology Assessments and Economic Evaluations 32 [CS search: P+I+Econ]
#26 #3 and #23 772
#27 #26 in Technology Assessments and Economic Evaluations 84 [ERG search: P+I]
#28 #27 not #25 52 [additional records missed by CS search]

Appendix 3: Summary and critique of the company's additional literature reviews ('targeted' literature review, HRQoL review, resource use and costs review)

Targeted literature search for studies informing the annual transition probability from non-cirrhotic to compensated cirrhosis health states

A search to identify reports of progression to cirrhosis for those with chronic hepatitis C was presented in Appendix 15 of the CS.[25] Embase (via Ovid) was the only database searched, and the presented strategy was reported in sufficient detail for the ERG to appraise the search. Database host and date of search was provided, however date span was not reported. Appendix 15 also reported that additional 'ad-hoc desk research' was conducted to supplement sources missed by the Embase search, however no further information was provided on what this entailed, where or how it was conducted.

The Embase strategy was structured in four facets representing the Disease, progression/natural history, genotype 3 and cirrhosis. As very few free-text synonyms or indexing terms were included in each of the facets, the ERG considered this search to be too restrictive. Searches presented in the clinical, cost-effectiveness, measurement and valuation of health effects and cost/healthcare resource identification sections included additional synonyms for hepatitis C that would have been beneficial to include in this targeted search. Appropriate Emtree indexing, such as Genotype/, Liver Cirrhosis/ and Disease Course/ could have been included in the strategy to improve its sensitivity. As the search involved a single database and failed to incorporate sufficient free-text or indexing, the ERG did not consider it adequate for this purpose.

Measurement and valuation of health effects

A search to identify health-related quality of life (HRQOL) studies relevant to the decision problem was conducted. Searches were reported for MEDLINE, MEDLINE In-Process, Embase, EconLit, CDSR, DARE, CENTRAL, HTA database and NHS EED. As reported for the cost-effectiveness searches, five conference proceedings were searched as PDFs or online. The CS and clarification response reported the host, date span and search dates for all resources. The searches were well reported and reproducible.

Medline, In-Process and Embase were searched concurrently using a combination of indexing and free-text. The ERG considered the approach appropriate, and noted it may have benefited from inclusion of additional free-text synonyms for chronic hepatitis C, which were presented in Appendix 3 in the clinical effectiveness strategies.

A facet of HRQOL terms was included in the NHS EED search. Although these terms were comprehensive, the ERG considered this limit to be overly restrictive when applied to small content-specific resources, such as NHS EED. The ERG reproduced the company's NHS EED search, minus the HRQOL terms. A test search conducted by the ERG using only the disease terms and limited to NHS EED content retrieved only 252 records.

Cost and healthcare resource identification, measurement and valuation

A search to retrieve references to resource allocation and chronic hepatitis C was conducted. Searches were reported for MEDLINE, MEDLINE In-Process, Embase, EconLit, HTA database and NHS EED, and limited by date to 2011-2016. The host, date span and search dates for all resources was reported in the CS[1] and response to clarification.[28] The searches were well reported and reproducible. The database searches were clearly structured and used combinations of index terms and free text.

The CS[25] reported inclusion of a facet to limit the Ovid searches to UK only, and referenced a strategy from the UK InterTASC ISSG Search Filter Resource.[104] This search was also limited using terms for cost and resource use based on a SIGN filter for economic studies. The ERG considered the Medline, In-Process and Embase search to be appropriate in structure and fit for purpose. The ERG had some concerns regarding the Cochrane Library search presented in Appendix 17.

Typographical errors were noted in the NHS EED strategy and in the confirmatory search in the clarification response.

There appeared to be a typographical error in line 37 of the strategy:[25]

37	**105-#36**	**67,387**

It is unclear whether this error occurred during the conduct or reporting of this search.

When the ERG queried inclusion of the economics filter in the NHS EED search, the company presented an updated strategy in the clarification response which contained a different error in the same line of the strategy, which may or may not have been a reporting error:[28]

37	**{or #4[105-#36]**	**67872**

A limited facet of resource allocation terms was included in the NHS EED search. When the ERG queried whether this limit was overly restrictive when applied to a small content-specific resource, such as NHS EED, the company presented a 'confirmatory' search to demonstrate no loss of records. The ERG accepted this response as adequate.

Appendix 4: Adjustments made to the model for the ERG base-case

Fixing errors

Correcting the transition probabilities calculated based on the literature by the company - required adjustment of:

- 'TPs default'!B2:B12
- TPs!M16:M36
- TPs!M42

Fixing violations

Incorporating an annual reinfection probability of 2.4% for the non-cirrhotic and (de)compensated cirrhosis states - required adjustment of:

- 'Inputs location'!A19:AZ20
- 'Inputs location'!A26:AZ26

Matters of judgment

Not applying the SVR utility increment for decompensated cirrhosis - required adjustment of:

- 'Utilities default'!B32
- Utilities!J166

The adjusted cells are marked with red font, using the adjusted values, in the model submitted by the ERG.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Thursday 4 August 2016** 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

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 10 "99% to 100% for GT2 (ASTRAL-2 and 3)" ASTRAL-3 does not report GT2	99% to 100% for GT2 (ASTRAL-1 and 2).	The current statement is inaccurate.	Corrected.

Issue 2

Description of problem	Description of proposed amendment			Justification for amendment	ERG response
Incorrect section or page numbers in the company submission cited.	ERG page number	Citation	Correction	The correct page numbers and sections will help to improve navigation between the ERG report and the company submission.	
	26	see CS, page 152	see CS, page 153		Not a factual inaccuracy: these are the page numbers in the report that the ERG received on 6th June 2016.
	28 (Table 4.2 footnotes)	Source: CS, Table 11, page 64, Table 43, page 151, and Table 44, page 152.	Source: CS, Table 11, page 64, Table 43, page 152, and Table 44, page 153.		
	37 (Table 4.6 footnotes)	Source: CS, Table 20, page 81; Table 21, page 83; and Table 22, page 84	Source: CS, Table 20, page 82; Table 21, page 83; and Table 22, page 84		
	40 (Table 4.7 footnotes)	Source: CS, Table 53, page 173.	Source: CS, Table 53, page 175.		

	41 (Table 4.8 footnotes)	Source: CS, Table 54, page 176.	Source: CS, Table 54, page 177.		
	42 (Table 4.9 footnotes)	Source: CS, Table 55, page 177.	Source: CS, Table 54, page 178.		
	50 (Table 5.2)	(Health related QoL row; column 4) Section 5.2.7	Section 5.4.2 and 5.4.6		Corrected.
	50 (Table 5.2)	(Resource utilisation and costs row; column 4) Section 5.2.2	Section 5.5.2, 5.5.3 and 5.5.4		Corrected.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 Formatting error creating a factual inaccuracy in Table 4.5 (Eligibility criteria): "HCV RNA≥104 IU/mL"	HCV RNA≥10^4 IU/mL	The current statement is inaccurate.	Corrected.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 62 LDV/SOF (8/12w) SVR values incorrectly reproduced for GT4/5/6 in Table 5.9: **TN** Non-CC: 94.4–100.0 CC: 83.3–100.0 **TE** Non-CC: 84.6 CC: 100.0	**TN** (amended values retrieved from table 117 in company submission) Non-CC: 94.4–96.0 CC: 96.0–100.0 **TE** (amended values retrieved from table 121 in company submission) Non-CC: 84.6–100.0 CC: 83.3–100.0	The current values are inaccurate.	Corrected.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 66, Table 5.11 1. Missing values in the GT1/1a/1b TN CC row for: • PR (24/48w) • SMV/PR • SOF/PR (12w)	1. GT1/1a/1b TN CC (amended values retrieved from table 104 in company submission) • PR (24/48w): -14.77 • SMV/PR: -14.27 • SOF/PR (12w): -14.52	The current values are inaccurate or missing.	The values are missing or inaccurate. This has been corrected.

2. DCC value incorrectly reported for SOF/VEL (12w)	2. Remove DCC value for SOF/VEL (12w) (see table 128 in company submission)		

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73, Table 5.16 ICER for SOF/VEL (12w) vs SOF/RBV (12/24w) incorrectly calculated as £1.6 mil for GT2 TE CC	**SOF/VEL (12w) vs SOF/RBV (12/24w) for GT2 TE CC** **SOF/VEL (12w)** / **SOF/RBV (12/24w)** **Costs** £46,851 / -£8,154 **QALYS** 9.76 / -0.01 **ICER** 815,400 (within the southwest quadrant)	The current value is inaccurate.	The QALY increment is not -0.01, but -0.00459. The ICER amounts to £1,774,628 (SW quadrant). This has been corrected.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.6 In relation to clinical effectiveness, the ERG report states “the main problem with [the] method of selecting inputs for the economic model still stands: using only one source for each intervention and population increases the chance	The approach taken to selecting inputs for the economic model has been adequately justified in the company submission in Table 39 and in response to relevant clarification questions acknowledging that the approach has provided ‘best available evidence’.	It is potentially misleading to suggest that the approach taken in the company submission to selecting inputs for the economic model increases the risk of bias and cherry-picking. As described in the company submission Table 39 and in response to relevant clarification questions, for the majority of	Not a factual inaccuracy: the ERG stands by the assertion that the selection of evidence was made according to the judgment of the company as opposed to by purely objective criteria or the synthesis of all evidence and as such poses a risk of bias.

of bias and cherry-picking.”		treatments in the economic model, only one relevant source of SVR data was available and therefore, an alternative approach (e.g. pooling of data from arms of relevant studies as suggested by the ERG) was not feasible. In cases where there was more than one potential source of SVR rate, the company has justified why the chosen source was considered most appropriate, and presented scenario analyses to clearly show that the use of alternative sources of SVR rate generally had no meaningful impact on the cost-effectiveness results. In relation to one of the model treatments (Peg-IFN+RBV 24 weeks in GT3), the company conducted a meta-analysis of available trials and showed that the chosen SVR rate for this treatment was conservative. This was described in full in response to clarification questions. Overall, we believe it is misleading to imply that the best available evidence may not have been utilised.	

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.4 In relation to the choice of SVR rates for the indirect comparison, the ERG suggests that the choice of SVR rate from different trials has been made arbitrarily, utilising an example of the Kowdley 2014 paper.	The approach taken to selecting inputs for the indirect comparison has been adequately justified in the company submission with an approach to provide 'best available evidence'; where multiple SVRs are available within one reference source, a conservative approach has been adopted.	Similar to the above point in relation to Section 4.6, it is potentially misleading to suggest that the approach taken in the company submission to selecting inputs for the indirect comparison increases the risk of bias and cherry-picking. In cases where there was more than one potential source of SVR rate, the company has justified why the chosen source was considered most appropriate including the situation where multiple SVRs are available within one reference source. Overall, we believe it is misleading to imply that the best available evidence may not have been utilised.	Not a factual inaccuracy: the ERG stands by the assertion that the selection of evidence was made according to the judgment of the company as opposed to by purely objective criteria or the synthesis of all evidence and as such poses a risk of bias.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.5 It is stated that separate subgroup analyses are not presented for patients who are intolerant to or ineligible for interferon treatment.	Cost-effectiveness results for patients who are ineligible for or unable to tolerate interferon are provided in the company submission (Sections 5.7.2.2, 5.7.2.7, 5.8.3.1 and 5.8.3.3)	The current statement is inaccurate.	Corrected.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.4 In relation to the imbalance in dropouts in the ASTRAL-3 trial, the ERG refutes the manufacturer's claim that this is to be expected by stating that "the ERG suggests this is unlikely as the intervention [i.e. SOF+RBV 24 weeks] is not one which is difficult or unpleasant to administer"	The observed imbalance in dropouts in the treatment arms in the ASTRAL-3 trial is in line with what would be expected in clinical practice.	It is factually incorrect to state that a treatment containing ribavirin is not one which is difficult or unpleasant to administer. The potential for patient discontinuation of treatment due to toxicity associated with ribavirin is clearly recognised with the ribavirin Summary of Product Characteristics (Section 4.8). In addition, the negative impact of ribavirin on patient Health-related Quality of Life is clearly demonstrated in the narrative summary of HRQL data from the ASTRAL-3 trial (Section 4.7.1.3 of the company submission) which refutes the assertion that this treatment is not difficult or unpleasant to administer. In addition, the ERG appears to agree with the manufacturer that the application of a utility decrement to patients receiving treatments containing ribavirin in the economic model is appropriate by stating that "Nevertheless, the ERG agrees that the on-treatment utility increments and decrements seem to reflect the direction of the	The ERG accepts that it is a difficult judgment as to what is 'unexpected' and so have changed the text in accordance with the company's request.

		effect of the different treatments on quality of life." (Section 5.2.7 of the ERG report)	

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6 In relation to the targeted literature review conducted by the manufacturer to identify the transition probability from the non-cirrhotic to compensated cirrhotic health states for use in the economic model, the ERG has stated that: “this search was not considered adequate by the ERG”.	The literature review conducted by the manufacturer identified a range of possible sources informing this transition probability. The manufacturer has appropriately justified the choice of transition probability for use in the economic model in the context of the sources identified.	It is potentially misleading to suggest that the targeted literature search conducted by the manufacturer was inadequate. As outlined in Section 5.3.2 of the company submission (Table 80), a large number of potentially relevant literature sources were identified to inform this model transition. The source of transition probability used in the model has been fully justified in the company submission, including validation by clinical expert opinion. It should be noted that the transition probability used in the economic model is conservative in the context of the available literature identified by the manufacturer in this targeted review (Table 80 of the company submission).	This is not a factual inaccuracy.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.7 The ERG has stated that 'The ERG acknowledges, and agrees with the company, that applying utility increments and decrements do not sensibly affect the results.' 'Sensibly' is not an appropriate term in this instance, and we suggest replacing with 'significantly'.	The ERG acknowledges, and agrees with the company, that applying utility increments and decrements do not significantly affect the results (response to the clarification letter Tables 35 to 38).	The current statement is inaccurate	This is not a factual inaccuracy.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.10 Regarding the implementation of the PSA, the ERG has stated that "…multiple comparators, which are considered consecutively in the probabilistic sensitivity analyses, are based on different 'random seeds', which is methodologically incorrect. It is common and efficient to implement a Markov model with an intervention and comparator model engine, and to re-run the model with alternative comparators for full incremental analysis, or for PSA. Controlling random numbers to remove Monte Carlo error is not always feasible for PSA and instead it is methodologically valid to ensure that sufficient simulations have been run to minimise Monte Carlo error. 1,000 simulations was found to be sufficient.	The model only allows comparison of SOF/VEL with one other comparator simultaneously. As a result, the multiple comparators, which are considered consecutively in the probabilistic sensitivity analyses, are based on different 'random seeds'. As not all relevant comparators identified in the final scope are incorporated in the base-case (see Table 5.16) and hence in the probabilistic sensitivity analyses, the probabilities of being cost effective presented in Table 5.18 might be overestimated.	It is potentially misleading to suggest that the implementation of PSA is methodologically incorrect.	This is not a factual inaccuracy.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3 "Moreover, the ERG did not perform probabilistic analyses because the economic model submitted by the company was unable to consider multiple comparators simultaneously in the probabilistic analyses (see section 5.2.10 for more details)." As mentioned in Issue 13, the model can account for multiple comparators in the probabilistic analyses, although we acknowledge that common random numbers are not utilised.	Recommend removing paragraph	It is potentially misleading to suggest that PSA with multiple comparators cannot be conducted using the economic model.	This is not a factual inaccuracy.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.4 "Also, the ERG did not perform probabilistic analyses because the economic model submitted by the company was unable to consider multiple comparators simultaneously in the probabilistic analyses (see section 5.2.10 for more details)." As mentioned in Issue 13, the model can account for multiple comparators in the probabilistic analyses, although we acknowledge that common random numbers are not utilised.	Recommend removing sentence.	It is potentially misleading to suggest that PSA with multiple comparators cannot be conducted using the economic model.	This is not a factual inaccuracy.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Sofosbuvir in combination with velpatasvir for treating chronic hepatitis C

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
10	Text changed: "99% to 100% for GT2 (ASTRAL-2 and 3)," to "99% to 100% for GT2 (ASTRAL-1 and 2),"
22	Text added: • "People who are ineligible for or unable to tolerate interferon" Text changed: "Separate subgroup analyses are not presented for patients who are co-infected with HIV, post-liver transplantation, and people who are intolerant to or ineligible for interferon treatment." to "Separate subgroup analyses are not presented for patients who are co-infected with HIV or post-liver transplantation."
29 30	Table 4.3, Astral-3, Were there any unexpected imbalances in drop-outs between groups? Text change: "Yes" to "No" Text change : "The ERG would suggest there were unexpected imbalances in dropouts between groups when comparing discontinuations of treatment. In contrast the CS states that the imbalances in dropouts are not unexpected and suggests the longer duration of treatment as a reason for the imbalance. The ERG suggests this is unlikely as the intervention is not one which is difficult or unpleasant to administer. The ERG cites Figure S2 in the supplementary appendix which illustrates that of the 280 randomised to receive SOF/RBV, 21 discontinued treatment due to adverse event (n=9); loss to follow-up (n=4), withdrew consent (n=3), death (n=2), non-compliance with study drug (n=2) and lack of efficacy (n=1). By comparison the SOF/VEL arm has two discontinuations (lack of efficacy and non-adherence) out of a possible 278.[31] For all other criteria the ERG agrees with the CS's assessment." to "For all criteria the ERG agrees with the CS's assessment."
33	Text changed: "HCV RNA≥104 IU/mL" to "HCV RNA≥10^4 IU/mL"
50	Text changed: "(Health related QoL row; column 4) Section 5.2.7" to "(Health related QoL row; column 4) Section 5.4.2 and 5.4.6"
50	Text changed: "Resource utilisation and costs row; column 4) Section 5.5.2" to "Resource utilisation and costs row; column 4) Section 5.5.2, 5.5.3 and 5.5.4"
62	Text changed: LDV/SOF (8/12w) SVR values for GT4/5/6 in Table 5.9: TN

	Non-CC: “94.4–100.0” to “94.4-96.0” CC: “83.3–100.0” to “96.0-100.0” TE Non-CC: “84.6” to “84.6-100.0” CC: “100.0” to “83.3-100.0”
66	The on-treatment utility increments for the following comparators in the GT1/1a/1b TN CC subgroup have been added in Table 5.11. Text added: • PR (24/48w): “-14.77” • SMV/PR: “-14.27” • SOF/PR (12w): “-14.52” The on-treatment utility increments for SOF/VEL (12w) in de DCC subgroup has been changed in Table 5.11. Text changed: - First row: “SOF/VEL (12w)” to “SOF/VEL (12w)[a]” - DCC on-treatment utility increment for SOF/VEL (12w)[a]: “4.43” to “-3.25” Text added: Key of Table 5.11: “[a] For DCC, this is SOF/VEL/RBV”
73	The results of the company base-case for SOF/RBV (12/24w) versus SOF/VEL (12wk) in the GT2 TE CC subgroups have been amended in Table 5.16. Text changed: - QALYs: “-0.01” to “>-0.00” - ICER: “£1.6 mil” to “£1.8 mil” The text in the first row, third column of Table 5.16 has been amended. Text changed: "Increments versus SOF/VEL (12w)" to “Increments for SOF/VEL (12w) versus comparator”
77	The text in the first row, third column of Table 5.17 has been amended. Text changed: "Increments versus SOF/VEL (12w)" to “Increments for SOF/VEL (12w) versus comparator”
88	The text in the first row, third column of Table 6.1 has been amended. Text changed: "Increments versus SOF/VEL (12w)" to “Increments for SOF/VEL (12w) versus comparator”

1. SUMMARY

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

The company's submission (CS) presents an evaluation of the clinical effectiveness and cost effectiveness of sofosbuvir-velpatasvir (SOF/VEL) for the treatment of chronic hepatitis C (CHC). The decision problem addressed by the CS was not completely in line with the final scope issued by the National Institute for Health and Care Excellence (NICE) with respect to the comparators. In particular, boceprevir and telaprevir are not included in the decision problem because these treatment regimens are no longer representative of current clinical practice according to the company.

The company's model does not include the development of resistance to SOF/VEL; the CS states that this was not considered in the economic model as this outcome does not impact the cost effectiveness of SOF/VEL, i.e. it has no impact on cost or QALYs.

1.2 Summary of clinical effectiveness evidence submitted by the company

The literature searches reported in the CS were well documented and easily reproducible. A good range of databases were searched, and additional searches of conference proceedings were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4.

Eighty-nine publications (reporting on 92 studies) were identified as meeting the eligibility criteria. Another 10 abstracts were identified from conference proceedings (eight additional studies plus one study reported in a full publication). Six of these publications/conference abstracts, representing seven studies, involved SOF/VEL. Three of these seven studies (ASTRAL-1 to 3) are reported by the company as the 'pivotal' RCTs.

The SOF/VEL trials included patients with all genotypes; treatment naïve and experienced patient populations; and patients with 'no cirrhosis and compensated cirrhosis'. In addition, ASTRAL-4 includes patients with decompensated cirrhosis.

SVR rates for SOF/VEL for 12 weeks were 98.1% for GT1a (ASTRAL-1), 99.2% for GT1b (ASTRAL-1), 99% to 100% for GT2 (ASTRAL-1 and 2), 95.3% for GT3 (ASTRAL-3), 100% for GT4 (ASTRAL-1), 97.1% for GT5 (ASTRAL-1), and 100% for GT6 (ASTRAL-1), infections. When split by cirrhosis status and previous treatment (naive or experienced), SVR rates were consistently above 95% for all genotypes, except for GT3. For patients with GT3, SVR rates were 98.2% for non-cirrhotic treatment-naive patients; 91.2% for non-cirrhotic treatment-experienced patients; 93.0% for cirrhotic treatment-naive patients; and 89.2% for cirrhotic treatment-experienced patients.

Health-related quality of life (HRQoL) questionnaires indicated no on-treatment decrements in HRQoL in SOF/VEL treated patients. According to the company, SOF/VEL has a favourable safety and tolerability profile. No adverse drug reactions specific to SOF/VEL were identified, with the type, incidence and severity of AEs being comparable to placebo.

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

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

ERG comment: The ERG's clinical expert agreed that indeed these two drugs were no longer used in clinical practice.

3.4 Outcomes

The CS[1] includes the following outcomes, all of which are specified in the final NICE scope[6]:

- SVR
- Mortality
- Adverse effects of treatment
- HRQoL

The CS does not include one of the outcomes specified in the NICE scope, that is, the development of resistance to sofosbuvir/velpatasvir, stating that this was not considered in the economic model as this outcome does not impact the cost effectiveness of SOF/VEL, i.e. it has no impact on cost or QALYs. Clinical advice received by the ERG suggests that this end point reflects treatment failure other than that from not taking pills. Given the high SVR rates this outcome may therefore be less relevant.

3.5 Other relevant factors

The decision problem addressed by the CS[1] includes consideration of the following subgroups, all of which were specified in the final NICE scope[21]:

- Genotype
- People with and without cirrhosis
- People with decompensated cirrhosis
- People who are ineligible for or unable to tolerate interferon

Separate subgroup analyses are not presented for patients who are co-infected with HIV or post-liver transplantation.

Regarding special considerations including issues related to equity or equality, the submission the submission states that CHC GT3 patients are characterised by a disproportionately higher number of patients from migrant backgrounds, which could potentially raise an equality issue if these people encounter greater difficulty in achieving access to SOF/VEL.

4.1.3 Critique of data extraction

For HRQoL studies, data extraction was performed independently by two reviewers (CS, Appendix 16.7, page 120); and for cost studies the data extraction process was not described (CS, Appendix 17). For effective studies it is not stated how many reviewers were involved in the data extraction process.

4.1.4 Quality assessment

Table 23 in section 4.6 of the CS[1] provided an overview of the quality assessment of the SOF/VEL RCTs. A complete quality assessment with supporting evidence of how the quality criteria were met was provided in Appendix 4.[25]

Table 4.1: Comparison of quality assessment of relevant RCTs by CS and ERG

	GS-US-342-1140 (ASTRAL-3) CHC GT3		GS-US-342-1139 (ASTRAL-2) CHC GT2		GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6	
	CS	**ERG**	**CS**	**ERG**	**CS**	**ERG**
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No	No	No	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	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	Yes	Yes

ERG comment: The ERG can find no reference to the criteria used to assess study quality e.g. the Cochrane Collaboration's tool for assessing risk of bias in randomised trials or similar.[43]

Appendix 4 of the CS states that in Astral-3 an Interactive Web Response System (IWRS) was employed to manage subject randomisation and treatment assignment. Demographic and baseline clinical characteristics were generally well balanced. As the study was open-label, care providers, participants and outcome assessors were not blinded to treatment allocation. There were greater number of dropouts in SOF/RBV treatment arm (n=21, vs. n=2 in SOF/VEL arm) and reasons for drop outs were provided. Authors of the CS state this difference may have been expected due to the use of RBV and the longer treatment duration in the SOF/RBV arm. Modified intention to treat (ITT) was used. The analyses assessed the patients that were randomised and received at least one dose of study drug (FAS) and appropriate methods were used to account for missing data.[25]

ERG comment: For all criteria the ERG agrees with the CS's assessment.

For Astral 2 again an interactive web response system was used. Demographic and baseline clinical characteristics were generally well balanced. The study was open-label. There were similar proportions of discontinuations in both treatment arms. Modified ITT was used and the analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data.[25]

ERG comment: The ERG agrees with the CS's quality assessment of Astral 2.

Finally for Astral 1 demographic and baseline clinical characteristics were generally well balanced. The study was conducted in a double blind manor. Study drugs were dispended to patients in a blinded fashion as directed by the interactive web response system. In the event of a medical emergency where breaking the blinding was required to provide medical care to the patient, the investigator may have obtained treatment assignment for that patient. If a patient's treatment assignment was disclosed to the investigator, study treatment was discontinued for the patient. There were similar proportions of discontinuations in both treatment arms. Modified ITT was used and the analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data.

ERG comment: The ERG agrees with the CS's quality assessment of Astral 1.

4.1.5 Evidence synthesis

In section 4.9 of the CS (page 104) the company states "Not applicable"

ERG comment: The ERG agrees that a meta-analysis of SOF/VEL trials is not feasible. The three main SOF/VEL RCTs included in the submission were all in different populations (ASTRAL-3: GT3; ASTRAL-2: GT2; and ASTRAL-1: GT1, GT2, GT4, GT5, and GT6). In addition, the comparators were different in the three trials (ASTRAL-3: SOF/RBV 24 weeks; ASTRAL-2: SOF/RBV 12 weeks; and ASTRAL-1: placebo). Therefore, the results from these studies cannot be pooled.

Table 4.2: Summary of trial methodology for comparative SOF/VEL RCTs

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
Study objective	To compare the efficacy of treatment with SOF/VEL for 12 weeks with that of SOF/RBV for 24 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 for 12 weeks with that of SOF/RBV for 12 weeks as measured by the proportion of patients with SVR12 To evaluate the safety and tolerability of each treatment regimen	To evaluate the efficacy of treatment with SOF/VEL for 12 weeks in patients with CHC as measured by the proportion of patients with SVR12 To evaluate the safety and tolerability of treatment with SOF/VEL for 12 weeks
Location	76 sites in the United States, Canada, Europe (France, Germany, Italy, and the United Kingdom), Australia, and New Zealand. 11 sites (105 patients) in the United Kingdom.	51 sites in the United States.	81 sites in the United States, Canada, Europe (France, Germany, Belgium, Italy and the United Kingdom), and Hong Kong. 11 sites (104 patients) in the United Kingdom.
Design	Multicentre, randomised, open-label, active controlled, Phase III.		Multicentre, randomised, double-blind, placebo-controlled, Phase III.
Duration of study	Treatment duration: 12 or 24 weeks depending on treatment assignment. Follow-up: up to 24 weeks.	Treatment duration: 12 weeks. Follow-up: up to 24 weeks.	Treatment duration: 12 weeks. Follow-up: up to 24 weeks.
Eligibility criteria	GT3	GT2	GT1, GT2, GT4, GT5, GT6 or indeterminate
	HCV treatment-naïve or treatment-experienced. Cirrhosis permitted: Approximately 20%. Inclusion: Aged ≥18 years; HCV RNA≥10^4 IU/mL 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. Exclusion: 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); prior exposure to SOF, NS5B or NS5A inhibitors; 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; clinically significant haemoglobinopathy. Contraindication to RBV (ASTRAL-2 and ASTRAL-3 only).		
Intervention(s)	Patients were randomised in a 1:1 ratio to:	Patients were randomised in a 1:1 ratio to:	Patients infected with HCV GT1, GT2, GT4 or

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
(n=) and comparator(s) (n=)	SOF/VEL for 12 weeks (n=277) SOF/RBV for 24 weeks (n=275) Patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily, or 400 mg of SOF once daily plus RBV. RBV was administered orally twice daily, with the dose determined according to body weight (1,000 mg daily in patients with a body weight <75 kg, and 1,200 mg daily in patients with a body weight ≥75kg).	SOF/VEL for 12 weeks (n=135) SOF/RBV for 12 weeks (n=134) Patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily, or 400 mg of SOF once daily plus RBV. RBV was administered orally twice daily, with the dose determined according to body weight (1,000 mg daily in patients with a body weight <75 kg, and 1,200 mg daily in patients with a body weight ≥75kg).	GT6: Randomised 5:1 to: SOF/VEL for 12 weeks (n=590) Placebo for 12 weeks (n=116) Patients in the placebo group were eligible for deferred treatment with SOF/VEL for 12 weeks. Patients infected with HCV GT5: Given the low prevalence of HCV GT5 infection, enrolment of only 20 patients was targeted for this group and 35 were eventually enrolled. These patients did not undergo randomisation and were pre-specified to receive SOF/VEL for 12 weeks. Patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily, or a placebo tablet to match the active treatment once daily.
Permitted and disallowed concomitant medications	Concomitant medications taken within 30 days of screening, up to and including 30 days after the last dose of study drug, were recorded. The following were prohibited from 28 days prior to the baseline/Day 1 visit through the EOT visit: Haematologic stimulating agents (e.g. ESAs, GCSF, TPO mimetics) Chronic systemic immunosuppressants including: Corticosteroids (prednisone equivalent of >10 mg/day for >2 weeks); Azathioprine; and Monoclonal antibodies (e.g. infliximab) Investigational agents or devices for any indication Drugs disallowed according to prescribing information of SOF or RBV (ASTRAL-2 and ASTRAL-3 only) Concomitant use of medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e. P-glycoprotein) which may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug(s) or these medications. Examples of representative medications that were prohibited from 21 days prior to baseline/Day 1 through EOT are listed in the clinical study protocol. Medications for disease conditions excluded from the protocol (e.g., HIV-1, active cancer, transplantation) were not listed as concomitant medications and were disallowed in the study.		

Trial no. (acronym)	GS-US-342-1140 (ASTRAL-3) CHC GT3	GS-US-342-1139 (ASTRAL-2) CHC GT2	GS-US-342-1138 (ASTRAL-1) CHC GT1, GT2, GT4–6
Primary outcomes	SVR12, defined as HCV RNA <LLOQ, 12 weeks after the end of treatment, in the FAS population. The LLOQ was 15 IU/mL.		
Secondary outcomes (including scoring methods and timings of assessments)	Proportion of patients with SVR (HCV RNA<LLOQ) at 4 weeks and 24 weeks after end of treatment (SVR4 and SVR24) The proportion of patients with HCV RNA<LLOQ on treatment by study visit HCV RNA change 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 Characterisation of drug resistance at baseline, during and after therapy: Deep sequencing of the HCV NS5A and NS5B coding regions was performed on samples obtained from all patients at baseline and again for all patients with virologic failure. Sequences that were obtained at the time of virologic failure were compared with sequences from baseline samples to detect resistance-associated variants that emerged during treatment. Resistance-associated variants that were present in >1% of sequence reads were reported. ALT normalisation HRQoL (SF-36, CLDQ-HCV, FACIT-F and WPAI)		

Source: CS, Table 12, page 65 and Table 13, page 70

Abbreviations: AE, adverse event; CHC, chronic hepatitis C; CLDQ, Chronic Liver Disease Questionnaire; CPT, Child-Pugh-Turcotte; CV, cardiovascular; ECG, electrocardiogram; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; FACIT-F, Fatigue Index; FAS, full analysis set; GCSF, granulocyte colony stimulating factor; GI, gastrointestinal; GT, genotype; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, Health Related Quality of Life; IFN interferon; INR, International Normalised Ratio; IWRS, interactive web response system; LLOQ, lower limit of quantitation; MELD, Model for End-Stage Liver Disease; RBV, ribavirin; RNA, ribonucleic acid; SF-36, 36-Item Short-Form Survey; SOF, sofosbuvir; SVR, sustained virologic response; TPO, thrombopoietin; VEL, velpatasvir; WPAI, Work Productivity and Activity Impairment

Table 5.3: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source / Justification	Signpost (location in CS)
Model	A Markov state-transition model was adapted from the model by Dusheiko and Roberts, 1995.[52] The same model structure is used for all patients irrespective of HCV genotype or treatment experience.	This model structure represents the natural history of CHC and has been widely used and adapted for HTA purposes.	Section 5.2.2.1 and 5.2.2.2
States and events	The following health states are incorporated in the model: • Non-cirrhotic • Compensated cirrhosis • Non-cirrhotic with SVR • Compensated cirrhosis with SVR • Decompensated cirrhosis • Decompensated cirrhosis with SVR • Hepatocellular carcinoma • Liver transplant • Post-liver transplant • Death	The health states earlier in disease progression than compensated cirrhosis are represented as a single health state (non-cirrhotic), rather than being separated 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. Moreover, this structure offers the best fit for the Gilead pivotal Phase III trials for SOF/VEL, in which patients were split between non-cirrhotic and cirrhotic defined as per the Fibrotest and Fibroscan scores.	Sections 5.2.2.1-5.2.2.3
Comparators	• 3D (12 w) • DCV/SOF (12w) • LDV/SOF (8/12w) • 2D/RBV (12/24w) • 3D/RBV (12/24w) • DCV/PR (48w)	The comparators DCV/SOF/RBV (12/24w) in GT3 cirrhotic patients, DCV/PR (48w) in GT4 patients, SMV/PR in GT4 patients and 2D 24w in GT4 for cirrhotic patients are listed in the scope, but are only included in scenario analyses. This is because the company considered	Section 5.2.3 and response to clarification question C

	Approach	Source / Justification	Signpost (location in CS)
	• DCV/SOF/RBV (12/24w) • LDV/SOF/RBV (12w) • PR (24/48w) • SMV/PR • SOF/PR (12w) • SOF/RBV (12/24w) • BSC	them to be irrelevant to clinical practice in the UK and/or to be always dominated.	
Population	People with chronic HCV. This population is subdivided by HCV genotype, previous treatment (treatment-naïve and treatment- experienced), cirrhosis state, and IFN eligibility.		Section 5.2.1
Treatment effectiveness	Incorporated using SVR rates		Section 4.10
Adverse events	Costs related to adverse events were considered.		Sections 5.5.4 and 5.6.1
Health related QoL	Health state utility values were obtained from Wright et al., 2006[53] and Ratcliffe et al., 2002[54] A utility increment, obtained from Vera-Llonch et al., 2013[55], is applied to patients who have achieved a SVR and utility increments and decrements are applied to health state utility values when patients are receiving treatment. These are based on different trials investigating treatments for CHC.[44, 56-59]	Utility values were elicited during the ASTRAL trials[31-33] through the SF-36 but were not used in the cost effectiveness model due to the unavailability of these data at the time of submission.	Section 5.4.2 and 5.4.6
Resource utilisation and costs	The following cost categories were considered • Drug costs • Monitoring costs • Health state costs • Adverse event costs		Section 5.5.2, 5.5.3 and 5.5.4

	Approach	Source / Justification	Signpost (location in CS)
Discount rates	Discount of 3.5% for utilities and costs	As per NICE scope	Section 5.2.2.4
Sub groups	Subgroups are defined based on HCV genotype, previous treatment, cirrhosis state and IFN eligibility.		Section 5.2.1
Sensitivity analysis	Both DSA and PSA are performed		Section 5.8

ADP = adenosine diphosphate; ASA = acetylsalicylic acid; BID = twice daily; CS = company submission; CV = cardiovascular; DSA = deterministic sensitivity analysis; EQ-5D = European Quality of Life-5 Dimensions; ICER = incremental cost effectiveness ratio; mg = milligram; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted Life Year; TIMI = Thrombolysis in Myocardial Infarction

Table 5.4: SVR (percentage) retrieved from CS Section 5.6.1

				Regimens not containing RBV/P				Regimens containing RBV/P								BSC
				SOF/VEL (12w)[a]	3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC[d]
GT1a	TN	non-CC	SVR	97.5[32]		100.0[70]	94.0[44]		97.0[71]				43.6[72]	82.0[73, 74]	91.7[58]		0.0
		CC	SVR	100.0[32]			94.1[56]		92.9[75]		100.0[76]		23.6[72]	60.4[73, 74]	80.8[58]		0.0
	TE	non-CC	SVR	97.5[32]		100.0[70]	95.4[57]		96.0[77]				17.6[78]	80.1[73, 74]	74.0[c]		0.0
		CC	SVR	100.0[32]			86.4[57]		95.4[75]		98.5[76]		10.0[78]	74.4[73, 74]	74.0[c]		0.0
GT1b	TN	non-CC	SVR	100.0[32]	99.0[71]	100.0[70]	94.0[44]						43.6[72]	82.0[73, 74]	91.7[58]		0.0
		CC	SVR	95.8[32]			94.1[56]		100.0[75]		100.0[76]		23.6[72]	60.4[73, 74]	80.8[58]		0.0
	TE	non-CC	SVR	100.0[32]	100.0[79]	100.0[70]	95.4[57]						17.6[78]	80.1[73, 74]	74.0[c]		0.0
		CC	SVR	95.8[32]			86.4[57]		97.8[75]		98.5[76]		10.0[78]	74.4[73, 74]	74.0[c]		0.0
GT1	TN	non-CC	SVR	98.4[e]		100.0[e]	94.0[e]						43.6[e]	82.0[e]	91.7[e]		0.0
				98.5[e]			94.1[e]		95.4[e]-		100.0[e]		23.6[e]	60.4[e]	80.8[e]		0.0
		CC	SVR						100.0[e]								
	TE	non-CC	SVR	98.4[e]		100.0[e]	95.4[e]						17.6[e]	80.1[e]	74.0[e]		0.0
		CC	SVR	98.5[e]			86.4[e]				100.0[e]		10.0[e]	74.4[e]	74.0[e]		0.0
GT2	TN	non-CC	SVR	99.0[31]									80.6[31, 58]			95.8[31]	0.0
		CC	SVR	100.0[31]									71.5[31, 58]			93.3[31]	0.0
	TE	non-CC	SVR	100.0[31]									35.0[80, 81]			81.3[31]	0.0
		CC	SVR	100.0[31]									35.0[80, 81]			100.0[31]	0.0
GT3	TN	non-CC	SVR	98.2[31]		77.8[17, 69]							71.2[82]		95.8[83]	90.4[31]	0.0
		CC	SVR	93.0[31]							57.9[f]		29.7[82]		91.3[83]	73.3[31]	0.0
	TE	non-CC	SVR	91.2[31]		71.4[17, 69]							35.0[80, 81]		94.2[83]	71.0[31]	0.0
		CC	SVR	89.2[31]							69.2[f]		35.0[80, 81]		85.7[83]	57.9[31]	0.0
				96.6-			94.4-	100.0[86]		81.2[87]			45.0[87]	84.4[88]	100.0[58]		0.0
GT4/5/6	TN	non-CC	SVR	100.0[32]			96.0[84, 85]										
				100.0[32]			96.0-	100.0[86]		77.8[87]			25.0[87]	66.7[88]	50.0[58]		0.0
		CC	SVR				100.0[84, 85]										
				100.0[32]			84.6-	100.0[86]		81.2[f]			45.0[f]	63.6[88]	100.0[58]		0.0
	TE	non-CC	SVR				100.0[84]										

		Regimens not containing RBV/P				Regimens containing RBV/P								BSC
		SOF/VEL (12w)[a]	3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC[d]
CC	SVR	100.0[32]			83.3-100.0[84]	100.0[86]		77.8[f]			25.0[f]	46.4[88]	50.0[58]		0.0
DCC[b]	SVR	94.3[33]							86.4[89]						

Abbreviations: TN, treatment naïve; TE, treatment experienced; SVR, sustained virologic response; DCC, Decompensated cirrhotic
[a]For DCC this is SOF/VEL/RBV
[b]Identical for TN and TE
[c]FDA analysis
[d]BSC SVR of 0% is based on an assumption
[e]Source not presented by the company
[f]Based on assumptions made by the company

Table 5.5: On-treatment utility increments and decrements for each subgroup (in percentage) (adapted from CS, Tables 93, 97, 103, 104, 108, 112, 116, 120,124 and 128)

Subgroups			Comparators														
			SOF/VEL (12w)[a]	2D/RBV (12w)	2D/RBV (24w)	3D (12 w)	3D/RBV (12w)	3D/RBV (24w)	DCV/SOF (12w)	DCV/SOF/RBV (12/24w)	LDV/SOF (8/12w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	SOF/VEL/RBV (12w)
GT1/1a/1b	TN	non-CC	4.43			4.43	-3.25		4.43		4.43		-14.77	-14.27	-14.52		
		CC	4.43				-3.25	-1		4.43	4.43		-14.77	-14.27	-14.52		
	TE		4.43			4.43	-3.25	-1	4.43		4.43		-14.77	-14.61	-14.52		
GT2*	TN		4.43										-14.77			-2.55	
	TE		4.43										-14.77			-6.88	
GT3*	TN		4.43						4.43	-3.25			-14.77		-14.52	-2.55	
	TE		4.43						4.43	-1			-14.77		-14.52	-6.88	
GT4/5/6*	TN		4.43	-3.25	-1						4.43		-14.77		-14.52		
	TE		4.43	-3.25	-1						4.43		-14.77		-14.52		
DCC			-3.25									-3.25					-3.25

GT= genotype; TN= treatment-naïve; TE= treatment-experienced; CC = cirrhotic; DCC = decompensated cirrhosis
* No difference made between cirrhotic and non-cirrhotic
[a] For DCC, this is SOF/VEL/RBV

Table 5.6: Company base-case results (discounted price for SOF/VEL unless stated otherwise) retrieved from CS Tables 129-170[a]

				Totals	Increments for SOF/VEL (12w) versus comparator[b]												
					Regimens not containing RBV/P			Regimens containing RBV/P									BSC
				SOF/VEL (12w)[b]	3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT1	**TN**	**non-CC**	**Costs**	£41,829[c]	[d]	-£20,554	**£12,116**		[d]				£20,949	£8,012	£498		£25,525
			QALYs	17.27		-0.05	**0.17**						2.05	0.66	0.29		3.64
			iCER			£411,080	**£71,271**						£10,219	£12,139	£1,717		£7,012
		CC	**Costs**	£59,495[c]			-£854		[d]		[e,f]		£15,918	£3,670	-£1,519		£23,705
			QALYs	10.11			0.23						3.75	1.95	0.95		5.13
			iCER				Dom						£4,245	£1,882	Dom		£4,621
	TE	**non-CC**	**Costs**	£41,176[c]	[d]	-£20,571	-£715		[d]				£19,764	£2,639	-£1,993		£25,844
			QALYs	16.27		-0.05	0.10						2.61	0.68	0.82		3.19
			iCER			£411,420	Dom						£7,572	£3,881	Dom		£8,102
		CC	**Costs**	£57,869[c]			-£2,419		[d]		[e,f]		£15,469	£350	-£2,774		£22,508
			QALYs	9.71			0.59						4.16	1.11	1.21		4.78
			iCER				Dom						£3,719	£315	Dom		£4,709
GT2	**TN**	**non-CC**	**Costs**	[redacted]									**£20,729**			[f]	£16,210
			QALYs										**0.63**				3.12
			iCER										**£32,903**				£5,196
		CC	**Costs**										£18,094			[f]	£12,619
			QALYs										1.46				5.20
			iCER										£12,393				£2,427
	TE	**non-CC**	**Costs**										£11,378			-£10,595	£16,394
			QALYs										1.82			0.53	2.77
			iCER										£6,252			Dom	£5,918
		CC	**Costs**										£7,740			-£8,154	£11,490
			QALYs										3.00			>-0.00	4.83
			iCER										£2,580			£1.8 mil	£2,379
GT3	**TN**	**non-CC**	**Costs**			[f]							£18,958				£12,590
			QALYs										1.24				4.41
			iCER										£15,289				£2,855

				Totals	Increments for SOF/VEL (12w) versus comparator[b]												
					Regimens not containing RBV/P			Regimens containing RBV/P									BSC
				SOF/VEL (12w)[b]	3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
		CC	Costs								[f]		£12,612		-£9,917	[f]	£14,020
			QALYs										3.24		0.11		4.84
			iCER										£3,893		Dom		£2,897
	TE	non-CC	Costs			[f]							£10,556		-£8,734		£14,144
			QALYs										2.21		-0.08		3.61
			iCER										£4,776		£109,175		£3,918
		CC	Costs								[f]		£9,766		-£9,857	[f]	£13,516
			QALYs										2.50		0.19		4.33
			iCER										£3,906		Dom		£3,121
GT4	TN	non-CC	Costs	£41,682[c]		[e,f]		**£5,490**		[e]			£21,172	[e]			£25,726
			QALYs	17.32				**0.01**					2.00				3.57
			iCER					**£549,000**					£10,586				£7,206
		CC	Costs				-£10,326	[e]		[e]	[e,f]		£5,268	[e]	-£18,223		£12,820
			QALYs				0.00						3.75		2.60		5.20
			iCER				Dom						£1,405		Dom		£2,465
	TE	non-CC	Costs	£41,046[c]		[e]	-£1,757	**£5,490**		[e]			£21,704	[e]			£26,048
			QALYs	16.32			0.48	**0.01**					1.76				3.14
			iCER				Dom	**£549,000**					£12,332				£8,296
		CC	Costs				-£10,317	[e]		[e]	[e,f]		£5,001	[e]	-£18,408		£11,617
			QALYs				0.00						3.49		2.43		4.85
			iCER				Dom						£1,433		Dom		£2,395
GT5	TN	non-CC	Costs										£10,958				£15,512
			QALYs										1.88				3.45
			iCER										£5,829				£4,496
GT6	TN	non-CC	Costs										£10,438				£14,992
			QALYs										2.00				3.57
			iCER										£5,219				£4,199
GT5/6[g]	TN	CC	Costs										£5,268		-£18,223		£12,820
			QALYs										3.75		2.60		5.20

				Totals	Increments for SOF/VEL (12w) versus comparator[b]											
					Regimens not containing RBV/P			Regimens containing RBV/P								BSC
				SOF/VEL (12w)[b]	3D (12 w)	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
			iCER										£1,405		Dom		£2,465
	TE	non-CC	Costs										£10,969				£15,313
			QALYs										1.76				3.14
			iCER										£6,232				£4,877
		CC	Costs										£5,001		-£18,408		£11,617
			QALYs										3.49		2.43		4.85
			iCER										£1,433		Dom		£2,395
DCC	TN		Costs									-£7,329					
			QALYs									0.16					
			iCER									Dom					
	TE		Costs									-£7,493					
			QALYs									0.15					
			iCER									Dom					

Abbreviations: TN, treatment naïve; TE, treatment experienced; Dom, dominance; iCER, incremental cost-effectiveness ratio; mil, million;

[a]To be consistent with the results presented in the CS, the incremental costs, QALYs and ICERs were recalculated by the ERG from the results presented in the CS. As a result, rounding errors might be induced. In addition, after consulting a clinical expert it was decided not to present the results for GT1a and GT1b but to present the results for the combined GT1 group only. This was done as it is consistent with the final scope and for reading convenience, given the amount of subgroups and comparators considered. Although there is some evidence of a differential response for GT1a and GT1b, this difference is small in magnitude and is unlikely to be a major issue from a clinical perspective.

[b]For DCC this is SOF/VEL/RBV

[c]Based on (anticipated) list price for SOF/VEL

[d]Only included for GT1a and/or GT1b by the company

[e]Only included in scenario analyses by the company

[f]Only presented by the company in the analysis for IFN ineligible patients

[g]The results for GT5 and GT6 were in part combined since these were identical.

Table 5.7: Company base-case results (discounted price for SOF/VEL unless stated otherwise) retrieved from CS Tables 129-170 and 225-238 and corrected by the ERG[a]

				Totals	Increments for SOF/VEL (12w) versus comparator[b]												
					Regimens not containing RBV/P			Regimens containing RBV/P									BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT1	**TN**	**non-CC**	**Costs**	£42,008[g]	**£4,500**	-£20,375	**£12,295**		**£2,907**				£21,128	£8,191	£677		£25,704
			QALYs	17.27	**-0.02**	-0.05	**0.17**		**0.07**				2.05	0.66	0.29		3.64
			iCER		**Dom**	£407,500	**£72,324**		**£41,529**				£10,306	£12,411	£2,334		£7,062
		CC	**Costs**	£59,674[g]			-£675		-£32,452		-£21,556[e]		£16,097	£3,849	-£1,340		£23,884
			QALYs	10.11			0.23		0.27		0.88[e]		3.75	1.95	0.95		5.13
			iCER				Dom		Dom		Dom[e]		£4,293	£1,974	Dom		£4,656
	TE	**non-CC**	**Costs**	£41,356[g]	**£4,110**	-£20,391	-£535		**£2,746**				£19,944	£2,819	-£1,813		£26,024
			QALYs	16.27	**-0.05**	-0.05	0.10		**0.09**				2.61	0.68	0.82		3.19
			iCER		**Dom**	£407,820	Dom		**£30,511**				£7,641	£4,146	Dom		£8,158
		CC	**Costs**	£58,048[g]			-£2,240		-£32,029		-£21,776[e]		£15,648	£529	-£2,595		£22,687
			QALYs	9.71			0.59		0.13		0.10[e]		4.16	1.11	1.21		4.78
			iCER				Dom		Dom		Dom[e]		£3,762	£477	Dom		£4,746
GT2	**TN**	**non-CC**	**Costs**	[redacted]									**£20,729**			-£8,665[e]	£16,210
			QALYs										**0.63**			0.11[e]	3.12
			iCER										**£32,903**			Dom[e]	£5,196
		CC	**Costs**	[redacted]									£18,094			-£9,375[e]	£12,619
			QALYs										1.46			0.35[e]	5.20
			iCER										£12,393			Dom[e]	£2,427
	TE	**non-CC**	**Costs**	[redacted]									£11,378			-£10,595	£16,394
			QALYs										1.82			0.53	2.77
			iCER										£6,252			Dom	£5,918
		CC	**Costs**	[redacted]									£7,740			-£8,154	£11,490
			QALYs										3.00			-0.01	4.83
			iCER										£2,580			£1.6 mil	£2,379

				Totals	Increments for SOF/VEL (12w) versus comparator[b]											
					Regimens not containing RBV/P			Regimens containing RBV/P								BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT3	**TN**	**non-CC**	**Costs**	£42,190[g]		-£23,951[e]							**£29,872**				£23,504
			QALYs	17.24		0.90[e]							**1.24**				4.41
			iCER			Dom[e]							**£24,090**				£5,330
		CC	**Costs**	£60,724[g]							-£27,470[e]		£23,526		£997	-£36,505[e]	£24,934
			QALYs	9.82							1.82[e]		3.24		0.11	0.97[e]	4.84
			iCER								Dom[e]		£7,261		£9,064	Dom[e]	£5,152
	TE	**non-CC**	**Costs**	£42,705[g]		-£23,833[e]							£21,470		£2,180		£25,058
			QALYs	15.98		0.78[e]							2.21		-0.08		3.61
			iCER			Dom[e]							£9,715		Dom		£6,941
		CC	**Costs**	£59,792[g]							-£24,859[e]		£20,681		£1,058	-£38,604[e]	£24,431
			QALYs	9.26							0.97[e]		2.50		0.19	1.47[e]	4.33
			iCER								Dom[e]		£8,272		£5,568	Dom[e]	£5,642
GT4	**TN**	**non-CC**	**Costs**	£41,862[g]		-£20,521[e]		**£5,670**		**£12,149**			£21,352	£8,416			£25,906
			QALYs	17.32		0.00[e]		**0.01**		**0.22**			2.00	0.62			3.57
			iCER			Dom[e]		**£567,000**		**£55,223**			£10,676	£13,574			£7,257
		CC	**Costs**	£59,524[g]			**£588**	-£32,602		-£825	-£25,127[e]		£16,182	£4,771	-£7,309		£23,734
			QALYs	10.18			**0.00**	0.34		0.30	1.89[e]		3.75	1.71	2.60		5.20
			iCER				**Dom**	Dom		Dom	Dom[e]		£4,315	£2,790	Dom		£4,564
	TE	**non-CC**	**Costs**	£41,226[g]		-£20,521	-£1,577	**£5,670**		-£665			£21,884	£362			£26,228
			QALYs	16.32		0.00	0.48	**0.01**		0.15			1.76	1.23			3.14
			iCER			Dom	Dom	**£567,000**		Dom			£12,434	£294			£8,353
		CC	**Costs**	£57,892[g]			**£597**	-£32,185		-£21,431	-£26,759[e]		£15,915	-£4,481	-£7,494		£22,531
			QALYs	9.78			**0.00**	0.20		1.02	1.49[e]		3.49	2.47	2.43		4.85
			iCER				**Dom**	Dom		Dom	Dom[e]		£4,560	Dom	Dom		£4,646
GT5	**TN**	**non-CC**	**Costs**	[redacted]									£10,958				£15,512
			QALYs										1.88				3.45
			iCER										£5,829				£4,496

				Totals	Increments for SOF/VEL (12w) versus comparator[b]											
					Regimens not containing RBV/P			Regimens containing RBV/P								BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT6	**TN**	**non-CC**	**Costs**	[redacted]									£10,438				£14,992
			QALYs										2.00				3.57
			iCER										£5,219				£4,199
GT5/6[f]	**TN**	**CC**	**Costs**	[redacted]									£5,268		-£18,223		£12,820
			QALYs										3.75		2.60		5.20
			iCER										£1,405		Dom		£2,465
	TE	**non-CC**	**Costs**	[redacted]									£10,969				£15,313
			QALYs										1.76				3.14
			iCER										£6,232				£4,877
		CC	**Costs**	[redacted]									£5,001		-£18,408		£11,617
			QALYs										3.49		2.43		4.85
			iCER										£1,433		Dom		£2,395
DCC	**TN**		**Costs**	[redacted]								-£7,329					
			QALYs									0.16					
			iCER									Dom					
	TE		**Costs**	[redacted]								-£7,493					
			QALYs									0.15					
			iCER									Dom					

Abbreviations: TN, treatment naïve; TE, treatment experienced; Dom, dominance; iCER, incremental cost-effectiveness ratio;
[a]To be consistent with the results presented in the CS, the incremental costs, QALYs and ICERs were recalculated by the ERG from the results presented in the CS. As a result, rounding errors might be induced. In addition, after consulting a clinical expert it was decided not to present the results for GT1a and GT1b but to present the results for the combined GT1 group only. This was done as it is consistent with the final scope and for reading convenience, given the amount of subgroups and comparators considered. Although there is some evidence of a differential response for GT1a and GT1b, this difference is small in magnitude and is unlikely to be a major issue from a clinical perspective.
[b]For DCC this is SOF/VEL/RBV. [c]Retrieved from GT1b subgroup. [d]Retrieved from GT1a subgroup. [e]Only presented by the company in the analysis for IFN ineligible patients.
[f]The results for GT5 and GT6 were in part combined since these were identical. [g]Based on (anticipated) list price for SOF/VEL.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Table 6.1: ERG base-case results (discounted price for SOF/VEL unless stated otherwise)

				Totals	Increments for SOF/VEL (12w) versus comparator[b]												
					Regimens not containing RBV/P			Regimens containing RBV/P									BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT1	**TN**	**non-CC**	**Costs**	£46,568[g]	**£4,471**	-£20,447	**£12,472**		**£2,969**				£23,643	£8,980	£978		£30,096
			QALYs	16.375	**-0.018**	-0.045	**0.131**		**0.053**				1.542	0.499	0.222		2.760
			iCER		**Dom**	£458,950	**£95,563**		**£56,005**				£15,334	£18,000	£4,405		£10,904
		CC	**Costs**	£64,906[g]			-£449		-£32,119		-£20,445[e]		£19,966	£5,831	-£430		£28,926
			QALYs	8.971			0.172		0.175		-0.057[e]		2.795	1.461	0.718		3.891
			iCER				Dom		Dom		£356,954[e]		£7,144	£3,991	Dom		£7,433
	TE	**non-CC**	**Costs**	£45,343[g]	**£4,047**	-£20,453	-£418		**£2,841**				£23,114	£3,675	-£862		£29,858
			QALYs	15.539	**-0.04**	-0.040	0.074		**0.075**				2.017	0.513	0.641		2.475
			iCER		**Dom**	£512,536	Dom		**£37,895**				£11,462	£7,157	Dom		£12,063
		CC	**Costs**	£63,139[g]			-£1,632		-£31,825		-£20,629[e]		£20,091	£1,844	-£1,368		£27,611
			QALYs	8.716			0.449		0.072		0.002[e]		3.177	0.802	0.931		3.688
			iCER				Dom		Dom		Dom[e]		£6,325	£2,299	Dom		£7,487
GT2	**TN**	**non-CC**	**Costs**	[redacted]									**£21,517**			-£8,538[e]	£20,194
			QALYs										**0.483**			0.088[e]	2.367
			iCER										**£44,545**			Dom[e]	£8,532
		CC	**Costs**	[redacted]									£19,585			-£9,033[e]	£17,736
			QALYs										1.091			0.269[e]	3.949
			iCER										£17,947			Dom[e]	£4,492
	TE	**non-CC**	**Costs**	[redacted]									£13,697			-£9,950	£19,894
			QALYs										1.398			0.409	2.136
			iCER										£9,798			Dom	£9,312

				Totals	Increments for SOF/VEL (12w) versus comparator[b]											
					Regimens not containing RBV/P			Regimens containing RBV/P								BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
		CC	Costs	[redacted]									£11,017			-£8,175	£16,467
			QALYs										2.273			0.000	3.727
			iCER										£4,846			Dom	£4,419
GT3	TN	non-CC	Costs	£47,476[g]		-£22,907[e]							**£31,297**				£28,527
			QALYs	16.158		0.691[e]							**0.949**				3.369
			iCER			Dom[e]							**£32,981**				£8,467
		CC	Costs	£65,673[g]							-£25,672[e]		£26,781		£1,085	-£35,462[e]	£29,694
			QALYs	8.757							1.379[e]		2.440		0.093	0.717[e]	3.677
			iCER								Dom[e]		£10,975		£11,662	Dom[e]	£8,076
	TE	non-CC	Costs	£47,029[g]		-£22,949[e]							£24,049		**£2,043**		£29,137
			QALYs	15.149		0.601[e]							1.707		**-0.057**		2.813
			iCER			Dom[e]							£14,088		**Dom**		£10,357
		CC	Costs	£64,416[g]							-£23,862[e]		£23,438		£1,231	-£37,009[e]	£28,888
			QALYs	8.372							0.744[e]		1.890		0.154	1.111[e]	3.343
			iCER								Dom[e]		£12,401		£7,982	Dom[e]	£8,640
GT4	TN	non-CC	Costs	£46,388[g]		[h]		**£5,670**		[h]			£23,838	[h]			£30,275
			QALYs	16.448		[h]		**0.014**		[h]			1.510	[h]			2.715
			iCER			[h]		**£393,002**		[h]			£15,783	[h]			£11,150
		CC	Costs	£64,830[g]			**£588**	£27,882		[h]	[h]		£20,057	[h]	-£4,749		£28,851
			QALYs	9.029			**0.000**	3.949		[h]	[h]		2.800	[h]	1.974		3.949
			iCER				**Dom**	£7,060		[h]	[h]		£7,162	[h]	Dom		£7,306
	TE	non-CC	Costs	£45,182[g]		[h]	-£990	**£5,670**		[h]			£24,059	[h]			£30,043
			QALYs	15.602		[h]	0.370	**0.014**		[h]			1.357	[h]			2.435
			iCER			[h]	Dom	**£393,002**		[h]			£17,734	[h]			£12,337
		CC	Costs	£63,057[g]			**£597**	£27,392		[h]	[h]		£19,702	[h]	-£4,993		£27,529
			QALYs	8.771			**0.000**	3.743		[h]	[h]		2.647	[h]	1.870		3.742
			iCER				**Dom**	£7,318		[h]	[h]		£7,442	[h]	Dom		£7,356

				Totals	Increments for SOF/VEL (12w) versus comparator[b]												
					Regimens not containing RBV/P			Regimens containing RBV/P									BSC
				SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC
GT5	**TN**	**non-CC**	**Costs**	[redacted]									£13,293				£19,730
			QALYs										1.418				2.623
			iCER										£9,376				£7,523
GT6	**TN**	**non-CC**	**Costs**	[redacted]									£12,923				£19,361
			QALYs										1.510				2.715
			iCER										£8,557				£7,130
GT5/6[f]	**TN**	**CC**	**Costs**	[redacted]									£9,142		-£15,664		£17,937
			QALYs										2.800		1.974		3.949
			iCER										£3,265		Dom		£4,542
	TE	**non-CC**	**Costs**	[redacted]									£13,145				£19,129
			QALYs										1.357				2.435
			iCER										£9,689				£7,855
		CC	**Costs**	[redacted]									£8,788		-£15,908		£16,615
			QALYs										2.647		1.870		3.742
			iCER										£3,319		Dom		£4,440
DCC	**TN**		**Costs**	[redacted]								-£7,721					
			QALYs									0.129					
			iCER									Dom					
	TE		**Costs**	[redacted]								-£7,852					
			QALYs									0.122					
			iCER									Dom					

Abbreviations: TN, treatment naïve; TE, treatment experienced; Dom, dominance; iCER, incremental cost-effectiveness ratio;

[a]After consulting a clinical expert it was decided not to present the results for GT1a and GT1b but to present the results for the combined GT1 group only. This was done as it is consistent with the final scope and for reading convenience, given the amount of subgroups and comparators considered. Although there is some evidence of a differential response for GT1a and GT1b, this difference is small in magnitude and is unlikely to be a major issue from a clinical perspective.

[b]For DCC this is SOF/VEL/RBV

[c]Retrieved from GT1b subgroup

	Totals	Increments for SOF/VEL (12w) versus comparator[b]											
		Regimens not containing RBV/P			Regimens containing RBV/P								BSC
	SOF/VEL (12w)[b]	3D (12 w)[c]	DCV/SOF (12w)	LDV/SOF (8/12w)	2D/RBV (12/24w)	3D/RBV (12/24w)[d]	DCV/PR (48w)	DCV/SOF/RBV (12/24w)	LDV/SOF/RBV (12w)	PR (24/48w)	SMV/PR	SOF/PR (12w)	SOF/RBV (12/24w)	BSC

[d]Retrieved from GT1a subgroup
[e]Only presented by the company in the analysis for IFN ineligible patients. Additionally, as the DCV/SOF/RBV comparator was not included for GT1 (CC) in the model received by the ERG, the ERG used DCV/SOF (12w) as a proxy for this comparator.
[f]The results for GT5 and GT6 were in part combined since these were identical.
[g]Based on (anticipated) list price for SOF/VEL
[h]This comparator was not included (for this specific subgroup) in the model received by the ERG and hence no results could be presented for the ERG base-case.

in collaboration with:

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Sofosbuvir in combination with velpatasvir for treating chronic hepatitis C ADDENDUM

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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This addendum contains the following additional analyses for the treatment naïve (TN) non cirrhotic (Non-CC) subgroups with genotype (GT) 2 and 3:

- A breakdown of the impact of the adjustments made by the ERG (correction of transition probabilities and including reinfection);
- Alternative estimates of treatment independent transition probabilities based on Fattovich, 1997[1] and Cardoso, 2010[2];
- Alternative calculation of treatment independent transition probabilities for the non-cirrhotic to compensated cirrhosis health state from Kanwal, 2014[3] based on adjusted hazard ratios.

The transition probabilities used in these analyses are presented in Table 1.

Table 1: Treatment independent transition probabilities

From	To	Population	Company base-case*	ERG base-case*	ERG base-case* corrected	Kanwal, 2014[3] adjusted HRs	Fattovich, 1997[1]
Non-cirrhotic	Compensated cirrhosis	GT2	0.0165	0.0167	As in CS	0.0145	NA
		GT3	0.0296	0.0305	As in CS	0.0276	NA
Compensated cirrhosis	Decompensated cirrhosis	GT1-6	0.0438	0.0425	0.0408	NA	0.039
	HCC	GT1-6	0.0631	0.0603	0.0568		0.014
Compensated cirrhosis SVR	Decompensated cirrhosis	GT1-6	0.0064	0.0063	0.0063		NA
	HCC	GT1-6	0.0128	0.0125	0.0124		NA
Decompensated cirrhosis	HCC	GT1-6	0.0631	0.0631	0.0568		0.014

Abbreviations: GT, genotype; HCC, hepatocellular carcinoma; SVR, Sustained virologic response; HRs, hazard ratios; NA, not available

*The transition probabilities from non-cirrhotic to compensated cirrhosis are taken from Kanwal, 2014[3]. All other transition probabilities are taken from Cardoso, 2010[2].

Unfortunately, the ERG made a mistake in correcting the treatment independent transition probabilities retrieved from Kanwal, 2014[3] and Cardoso, 2010[2]. The calculation of the probabilities from Kanwal, 2014[3] by the company is correct. Although the probabilities the company uses from Cardoso, 2010[2] are equal to the probabilities used from this source in STA363, the ERG calculated different probabilities from this same source. The newly calculated transition probabilities by the ERG are lower. In TA331, the transition probability for CC with SVR to HCC was also taken from Cardoso. The company estimated the value to be 0.005, but this was corrected to 0.0123 by the ERG (in TA331). We now arrive at a value of 0.0124. All other treatment independent transition probabilities from Cardoso have not been used in previous TAs (Fattovich, 1997[1] or assumptions were used instead).

As can be seen in Tables 2a and 2b, the original correction of the transition probabilities had very little impact on the results. The difference between the company and the original ERG's base-case was almost entirely caused by including reinfection. This is also the case for the corrected ERG's base-case with corrected values for the transition probabilities based on Cardoso, 2010[2] and using the estimations from Kanwal, 2014[3] from the company base-case.

Table 2a: Breakdown of impact of adjustments for the ERG base-case for the GT 3 TN Non-CC subgroup

		Totals			**Increments for SOF/VEL (12w) versus comparator**	
		SOF/VEL (12w)[#]	**PR (24/48w)**	**BSC**	**PR (24/48w)**	**BSC**
Company base-case (table 1 column 4)	**Costs**	[redacted]	[redacted]	[redacted]	**£18,958**	£12,590
	QALYs				**1.247**	4.412
	iCER				**£15,199**[a]	£2,854[b]
1. Correction of transition probabilities (table 1 column 5)	**Costs**	[redacted]	[redacted]	[redacted]	**£18,888**	£12,331
	QALYs				**1.259**	4.454
	iCER				**£15,007**	£2,769
2. Including reinfection	**Costs**	[redacted]	[redacted]	[redacted]	**£20,433**	£17,802
	QALYs				**0.941**	3.337
	iCER				**£21,724**	£5,334
ERG-base-case (1 & 2)	**Costs**	[redacted]	[redacted]	[redacted]	**£20,383**	£17,613
	QALYs				**0.949**	3.369
	iCER				**£21,479**	£5,228
3. Correction of transition probabilities #2 (table 1 column 6)	**Costs**	[redacted]	[redacted]	[redacted]	**£18,943**	£12,531
	QALYs				**1.225**	4.327
	iCER				**£15,468**	£2,896
Corrected ERG base-case (2 & 3)	**Costs**	[redacted]	[redacted]	[redacted]	**£20,416**	£17,737
	QALYs				**0.924**	3.274
	iCER				**£22,099**	£5,418

Abbreviations: QALY = quality-adjusted life year; ICER = incremental cost effectiveness ratio; TP, transition probability. [a] retrieved from the cost-effectiveness model; the ERG reports £15,289 in Table 5.16 of the ERG report because of rounding. [b] retrieved from the cost-effectiveness model; the ERG reports £2,855 in Table 5.16 of the ERG report because of rounding.[#] In a full incremental analysis, SOF/VEL is compared to PR.

Table 2b: Breakdown of impact of adjustments for the ERG base-case for the GT 2 TN Non-CC subgroup

		Totals			Increments for SOF/VEL (12w) versus comparator	
		SOF/VEL (12w)[#]	PR (24/48w)	BSC	PR (24/48w)	BSC
Company base-case (table 1 column 4)	**Costs**	[redacted]	[redacted]	[redacted]	**£20,729**	£16,210
	QALYs				**0.636**	3.128
	iCER				**£32,595**[a]	£5,183[b]
1. Correction of transition probabilities (table 1 column 5)	**Costs**	[redacted]	[redacted]	[redacted]	**£20,708**	£16,095
	QALYs				**0.637**	3.136
	iCER				**£32,486**	£5,132
2. Including reinfection	**Costs**	[redacted]	[redacted]	[redacted]	**£21,533**	£20,282
	QALYs				**0.482**	2.360
	iCER				**£44,682**	£8,593
ERG-base-case (1 & 2)	**Costs**	[redacted]	[redacted]	[redacted]	**£21,517**	£20,194
	QALYs				**0.483**	2.367
	iCER				**£44,545**	£8,532
3. Correction of transition probabilities #2 (table 1 column 6)	**Costs**	[redacted]	[redacted]	[redacted]	**£20,723**	£16,179
	QALYs				**0.626**	3.074
	iCER				**£33,099**	£5,264
Corrected ERG base-case (2 & 3)	**Costs**	[redacted]	[redacted]	[redacted]	**£21,527**	£20,246
	QALYs				**0.475**	2.319
	iCER				**£45,348**	£8,729

Abbreviations: QALY = quality-adjusted life year; ICER = incremental cost effectiveness ratio; TP, transition probability. [a] retrieved from the cost-effectiveness model; the ERG reports £32,903 in Table 5.16 of the ERG report because of rounding. [b] retrieved from the cost-effectiveness model; the ERG reports £5,196 in Table 5.16 of the ERG report because of rounding.[#] In a full incremental analysis, SOF/VEL is compared to PR.

The results of the additional analyses (including reinfection, using Fattovich, 1997[1], and using transition probabilities from Kanwal, 2014[3] based on adjusted hazard ratios), with the company base-case as starting point, are shown in Table 3a and 3b. In these tables, for completeness, also the ERG analysis with corrected transition probabilities (as shown in column 6 in table 1) is included. Furthermore, the combined results of these adjustments are shown.

In the company's and the ERG's base-case the transition probabilities from Kanwal, 2014[3] were based on the reported incidence rates per 1,000 person-years. In this study, also a Cox proportional hazards models to examine the association between HCV genotype and time to cirrhosis while adjusting for potential confounders is presented. The ERG now feels that it is more appropriate to use the adjusted hazard ratios (0.68 and 1.38 for GT2 and GT3 versus GT1, respectively) to calculate the genotype specific transition probability from no cirrhosis to compensated cirrhosis. These transition probabilities are lower than the values that were used in the company's and the ERG's base-case (Table 1).

All adjustments increase the incremental cost effectiveness ratios. The largest increase is due to the inclusion of reinfection.

Table 3a: Deterministic results of additional analyses of SOF/VEL versus comparators for the GT 3 TN Non-CC subgroup

		Totals			**Increments for SOF/VEL (12w) versus comparator**	
		SOF/VEL (12w)[#]	**PR (24/48w)**	**BSC**	**PR (24/48w)**	**BSC**
Company base-case (table 1 column 4)	**Costs**	[redacted]	[redacted]	[redacted]	**£18,958**	£12,590
	QALYs				**1.247**	4.412
	iCER				**£15,199**[a]	£2,854[b]
1. Including reinfection	**Costs**	[redacted]	[redacted]	[redacted]	**£20,433**	£17,802
	QALYs				**0.941**	3.337
	iCER				**£21,724**	£5,334
2. Including TPs from Fattovich, 1997[1] (table 1 column 8)	**Costs**	[redacted]	[redacted]	[redacted]	**£18,537**	£11,005
	QALYs				**1.057**	3.703
	iCER				**£17,540**	£2,972
3. Including Kanwal, 2014[3] TPs based on adjusted HRs (table 1 column 7)	**Costs**	[redacted]	[redacted]	[redacted]	**£19,099**	£13,109
	QALYs				**1.199**	4.234
	iCER				**£15,923**	£3,096
Including 2 & 3	**Costs**	[redacted]	[redacted]	[redacted]	**£18,701**	£11,612
	QALYs				**1.018**	3.560
	iCER				**£18,362**	£3,262
Including 1, 2 & 3	**Costs**	[redacted]	[redacted]	[redacted]	**£20,197**	£16,892
	QALYs				**0.770**	2.689
	iCER				**£26,239**	£6,282
4. Correction of transition probabilities #2 (table 1 column 6)	**Costs**	[redacted]	[redacted]	[redacted]	**£18,943**	£12,531
	QALYs				**1.225**	4.327
	iCER				**£15,468**	£2,896
Including 1, 2, 4 (Corrected ERG base-case with TPs from Fattovich, 1997)	**Costs**	[redacted]	[redacted]	[redacted]	**£20,082**	£16,458
	QALYs				**0.798**	2.797
	iCER				**£25,157**	£5,884
Including 1 – 4[c]	**Costs**	[redacted]	[redacted]	[redacted]	**£20,197**	£16,892
	QALYs				**0.770**	2.689
	iCER				**£26,239**	£6,282

Abbreviations: QALY = quality-adjusted life year; ICER = incremental cost effectiveness ratio; TP, transition probability; CS, company submission. [a] retrieved from the cost-effectiveness model; the ERG reports £15,289 in Table 5.16 of the ERG report because of rounding. [b] retrieved from the cost-effectiveness model; the ERG reports £2,855 in Table 5.16 of the ERG report because of rounding. [c] The results of the analysis combining 1-3 is equal to 1-4 because the corrected transition probabilities for compensated cirrhosis with SVR to decompensated cirrhosis and hepatocellular carcinoma from Cardoso, 2010 are not of influence in the no cirrhosis subgroup. [#] In a full incremental analysis, SOF/VEL is compared to PR.

Table 3b: Deterministic results of additional analyses of SOF/VEL versus comparators for the GT 2 TN Non-CC subgroup

		Totals			Increments for SOF/VEL (12w) versus comparator	
		SOF/VEL (12w)[#]	PR (24/48w)	BSC	PR (24/48w)	BSC
Company base-case (table 1 column 4)	**Costs**	[redacted]	[redacted]	[redacted]	**£20,729**	£16,210
	QALYs				**0.636**	3.128
	iCER				**£32,595**[a]	£5,183[b]
1. Including reinfection	**Costs**	[redacted]	[redacted]	[redacted]	**£21,533**	£20,282
	QALYs				**0.482**	2.360
	iCER				**£44,682**	£8,593
2. Including TPs from Fattovich, 1997[1] (table 1 column 8)	**Costs**	[redacted]	[redacted]	[redacted]	**£20,566**	£15,244
	QALY				**0.554**	2.675
	iCER				**£37,125**	£5,699
3. Including Kanwal, 2014[3] TPs based on adjusted HRs (table 1 column 7)	**Costs**	[redacted]	[redacted]	[redacted]	**£20,859**	£16,923
	QALYs				**0.594**	2.899
	iCER				**£35,091**	£5,837
Including 2 & 3	**Costs**	[redacted]	[redacted]	[redacted]	**£20,705**	£16,061
	QALYs				**0.520**	2.492
	iCER				**£39,783**	£6,446
Including 1, 2 & 3	**Costs**	[redacted]	[redacted]	[redacted]	**£21,495**	£20,052
	QALYs				**0.396**	1.872
	iCER				**£54,237**	£10,710
4. Correction of transition probabilities #2 (table 1 column 6)	**Costs**	[redacted]	[redacted]	[redacted]	**£20,723**	£16,179
	QALYs				**0.626**	3.074
	iCER				**£33,099**	£5,264
Including 1, 2, 4 (Corrected ERG base-case with TPs from Fattovich, 1997)	**Costs**	[redacted]	[redacted]	[redacted]	**£21,390**	£19,457
	QALYs				**0.421**	2.013
	iCER				**£50,812**	£9,666
Including 1 – 4[c]	**Costs**	[redacted]	[redacted]	[redacted]	**£21,495**	£20,052
	QALYs				**0.396**	1.872
	iCER				**£54,237**	£10,710

Abbreviations: QALY = quality-adjusted life year; ICER = incremental cost effectiveness ratio; TP, transition probability. [a] retrieved from the cost-effectiveness model; the ERG reports £32,903 in Table 5.16 of the ERG report because of rounding. [b] retrieved from the cost-effectiveness model; the ERG reports £5,196 in Table 5.16 of the ERG report because of rounding. [c] The results of the analysis combining 1-3 is equal to 1-4 because the corrected transition probabilities for compensated cirrhosis to decompensated cirrhosis with SVR and hepatocellular carcinoma from Cardoso, 2010 are not of influence in the no cirrhosis subgroup. [#] In a full incremental analysis, SOF/VEL is compared to PR.

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