NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Glecaprevir with pibrentasvir for treating chronic hepatitis C [ID1085]

Contents:

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

Pre-meeting briefing

Glecaprevir/pibrentasvir for treating chronic hepatitis C

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

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

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

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

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

COMMON ABBREVIATIONS (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
EBR	elbasvir
GT	genotype
GP	glecaprevir-pibrentasvir
GZR	grazoprevir
LDV	ledipasvir
NC	no cirrhosis
OPR	ombitasvir/paritaprevir/ritonavir
PR	peginterferon and ribavirin
R	ribavirin
SMV	simeprevir
SOF	sofosbuvir
SVR	sustained viralogical response
TE	treatment-experienced
TN	treatment naïve
TVR	telaprevir
VEL	velpatasvir

Key Issues

1. Have the appropriate comparators been included by the company (slide 7)?
2. What conclusions can be drawn from the results of the naïve indirect comparison given the ERG's concerns that the number of patients in the trials are very low and the choice of SVR rates are from only 1 source?
3. Where applied, does the committee accept the use of similar modelling assumptions and subgroup analysis as for previous Hep C appraisals?
   - Comparator SVR 12 rates
   - Model structure
   - Fibrosis progression
   - Non fibrosis progression
   - Liver transplant to death
4. Is the use of Wright et al (same as TA430) for HRQoL values appropriate considering there is trial data available?
5. What is the most plausible ICER based on the committee's preferred assumptions?
6. Is glecaprevir-pibrentasvir an innovative treatment?
7. Potential equality issues?

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

RELEVANT NICE TECHNOLOGY APPRAISALS

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

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

DETAILS OF THE TECHNIOLOGY	
Technology	Glecaprevir/pibrentasvir (Maviret, AbbVie)
Marketing authorisation	For the treatment of chronic hepatitis C virus (HCV) infection in adults • All genotypes GT1-GT6 • No cirrhosis and compensated cirrhosis • Treatment naive and Treatment experienced* *(previous treatment does not include an NS5A and/or NS3/4A inhibitor)*
Mechanism of action	Fixed dose combination of 2 DAAs: • glecaprevir inhibits HCV NS3/4A protease • pibrentasvir inhibits HCV non-structural protein 5a (NS5A)
Administration	Oral, 100 mg/ 4 mg 3 tablets administered once daily: • 8 weeks (TN, NC, all genotypes) • 8 weeks (TE, NC, GT1, 2, 4-6) • 12 weeks (TN, CC, all genotypes) • 12 weeks (TE, CC, GT1, 2, 4-6) • 16 weeks (TE, NC or CC, GT3)
Acquisition cost	List price per pack: £12,993.99 • £25,987.32 for 8 weeks treatment • £38,980.98 for 12 weeks treatment • £51,974.64 for 16 weeks treatment The company have agreed a confidential pricing agreement with the commercial medicines unit

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.	Glecaprevir-pibrentasvir		
Com.	• BSC (GT1-6) • DCV + SOF, with or without RBV (GT1, 3 or 4) • EBR/GZR (GT1 or 4) • LDV/SOF (GT1 or 4) • OBV/PTV/RTV with or without DSV or RBV (GT1 or 4) • PegIFNα + RBV (GT1– 6) • SOF + RBV, with or without pegIFNα (GT1–6) • SOF + VEL (GT1-6)	• BSC (GT1-6) • DCV + SOF **without RBV (for GT3 only)** • EBR/GZR (GT1 or 4) • LDV/SOF (GT1 or 4) • OBV/PTV/RTV with or without DSV or RBV (GT1 or 4) • PegIFNα + RBV **GT2 (NC TN)** • SOF + RBV, with or without pegIFNα **(GT2, 3, 5 and 6)** • SOF + VEL (GT1-6)	• Excluded comparators not used in current NHS practice
Out.	• sustained virological response (SVR) • resistance to treatment • mortality • adverse effects of treatment • health-related quality of life	Resistance not modelled	Resistance does not impact costs or QALYs

Submissions from patient/carer organisations

Hepatitis C Trust

- People with Hepatitis C can experience:
  - Differing symptoms, from mild to debilitating (chronic fatigue, mood swings, sexual dysfunction)
  - Liver damage even with mild symptoms
  - Stigma from association with drug misuse, potentially leading to employment discrimination
  - Anger when infected through NHS
- Glecaprevir-pibrentasvir:
  - Could end the use of PegIFNα which can cause significant long term harm
  - Retreatment for people whose prior treatment with DAAs failed
  - Offers another pan genotypic treatment option for hepatitis c

Submissions from professional groups and clinical experts

Submissions from; British Society of Gastroenterology, Royal College of Pathologists, UK Clinical Pharmacy Association, 2 x clinical experts:

- The is an important pan-genotypic treatment
- Short treatment duration (8 weeks for some subgroups)
- Can improve life expectancy for following groups:
  - Retreatment for people in subgroups GT 1 and 4 whose prior treatment with DAAs failed
  - People with renal failure (specifically those with GT 3,5-6 who currently have no treatment options)
  - GT 3 treatment failures with Peg interferon and RBV ± sofosbuvir regimens)
- Few side effects of treatment
- The regimen is contraindicated for patients with decompensated cirrhosis

Clinical effectiveness - trials (I)

Trial	Pop.	Int/com	Primary outcome
ENDURANCE-1 • Phase III • Randomised • Open label • Multicentre	• GT 1 • TN or TE-PRS • NC • HIV-1 (with/without) • Treatment length 8 or 12 weeks	randomised in a 1:1 ratio to: • G/P for 12 weeks (n=352) • G/P for 8 weeks (n=351)	• Non-inferiority of the % patients in the 12-week arm ITT achieving Sustained virologic response 12 weeks after treatment (SVR12)
ENDURANCE-3 • Phase III • Partially randomised • Open label • Active controlled • multicentre	• GT 3 • TN • NC • Treatment length 8 or 12 weeks	randomised in a 2:1 ratio to: • G/P for 12 weeks (n=233) • SOF + DCV for 12 weeks (n=115) After enrolment completion, new patients were assigned to receive G/P for 8 weeks (n=157)	• Non-inferiority of the % patients in the ITT achieving SVR12 in the G/P 12-week arm vs the SOF + DCV 12-week arm • Non-inferiority of the % patients in the ITT achieving SVR12 in the G/P 8-week arm vs G/P 12-week arm
EXPEDITION-1 • Phase III • Single arm • Open label • Multicentre	• GT 1, 2, 4 - 6 • TN or TE-PRS • CC • Treatment length 8 or 12 weeks	• G/P for 12 weeks (n=146)	• % patients in the ITT population achieving SVR12

Clinical effectiveness - trials (II)

Trial	Pop.	Int/Com	Primary outcome
SURVEYOR-II (Part 1) • Phase II • Randomised • Open label • Multicentre	• GT 2 or 3 • TN or TE-PRS • NC • G/P treatment length 12 weeks	GT2 NC patients randomised in a 1:1:1 ratio to: • G/P (300 mg/120 mg) for 12 weeks (n=25) • G/P (200 mg/120 mg) for 12 weeks (n=24) • G/P (200 mg/120 mg) + RBV for 12 weeks (n=25) GT3 NC patients were randomised in a 1:1:1:1 ratio to: • G/P (300 mg/120 mg) for 12 weeks (n=30) • G/P (200 mg/120 mg) for 12 weeks (n=31) • G/P (200 mg/120 mg) + RBV for 12 weeks (n=31) • G/P (200 mg/40 mg) for 12 weeks (n=30)	• % in the ITT achieving SVR12.
SURVEYOR-II (Part 2) • Phase II • Open label • Partially randomised • Multicentre	• GT 2 or 3 • TN or TE-PRS • NC or CC (GT3 CC were TN only; GT2 were NC only) • G/P treatment length: 8 or 12 weeks ± RBV	• GT2 NC patients received G/P for 8 weeks (n=54) • GT3 NC patients received G/P for 8 (TN) or 12 (TE-PR) weeks (n=53) GT3 TN CC patients were randomised in a 1:1 ratio to: • G/P for 12 weeks (n=28) • G/P + RBV for 12 weeks (n=27)	

Clinical effectiveness - trials (III)

Trial	Pop.	Int/Com	Primary outcome

SURVEYOR-II (Part 3)
• Phase II
• Open label
• Partially randomised
• Multicentre
	• GT 3
	• TN
	• NC
	• Treatment length 8 or 12 weeks
		• TE-PRS patients without cirrhosis were randomised at a 1:1 ratio to:
		  • G/P for 12 weeks (n=22)
		  • G/P for 16 weeks (n=22)
		• TN CC received G/P for 12 weeks (n=40)
		• TE-PRS CC received G/P for 16 weeks (n=47)
			• % in the ITT achieving SVR12.

SURVEYOR-II (Part 4) • Phase II • Open label • Partially randomised • Multicentre	• GT 2, 4-6 • TN or TE-PRS • NC • Treatment length 8 weeks	• Patients received 3 fixed-dose combination tablets containing 100 mg of GLE and 40 mg of PIB • GT2 (n=145) • GT4, GT5 or GT6 (n=58)	• Non-inferiority of the % of GT2 TN NC patients in the ITT population achieving SVR12 compared to the historical efficacy (SVR12 95%) of 12-week treatment with SOF + RBV

Clinical effectiveness results (I)

- Results presented by the company are non-comparative except for the comparison in ENDURANCE-3 for G/P and SOF+DCV which showed that G/P 12 weeks was non-inferior to SOF + DCV by analysis of both ITT and per protocol populations.
- % of patients achieving SVR 12 ranged from [redacted]
- The data were presented by genotype, treatment status and cirrhosis status.

ERG comments:

- Noted that for GT4-6 the number of patients in the trials are very low (some less than 10 patients in each group).
- Only 4 out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore there is considerable uncertainty around SVR rates in most subgroups.

Results on slides 16-18

Adverse effects of treatment

- The SmPC lists headache and fatigue as the most common adverse effects.
- In Endurance II (placebo controlled) with GT 2 NC TN or TE there was a [redacted]
- In Endurance III (active controlled). G/P had a [redacted]
- In 21 arms of the phase II/III studies who have received at least 1 dose of G/P (300 mg/120 mg without RBV):
  - [redacted] experienced any drug related adverse events
  - Out of the [redacted] patients who experienced an AE of grade 3 or above [redacted] patients had AEs considered study drug-related ([redacted]) patient each with [redacted]

The frequency of serious AEs and grade ≥3 AEs was [redacted]

Indirect treatment comparison

- The company identified 1 trial providing direct head-to-head evidence for G/P compared with SOF/DCV (ENDURANCE-3)
- The company did not identify any trials comparing G/P to the other comparators listed in the NICE scope.
- The company used a naïve indirect comparison, using the same SVR rates for comparator technologies that had been identified in a previous NICE technology appraisal guidance (TA430 sofosbuvir-velpatasvir for treating chronic hepatitis C).

ERG comments

- The ERG acknowledged that the company had followed the same methodology which had been accepted in previous NICE guidance on HCV and highlighted that the same limitations with this approach apply:
  - Company selected sources for SVR rates of comparator technologies which results in bias similar to observational studies
  - Other study designs could have been included in the company's literature search including uncontrolled studies and case series
  - When multiple SVR rates were presented within a study the company selected only one SVR rate to include in the analysis

SVR12 RATES % (n [where reported]) used in company model					
		TN		TE	
GT	Treatment	NC	CC	NC	CC
1	G/P	[redacted]	[redacted]	[redacted]	[redacted]
	SOF/VEL	98.4% (251/255)	98.6% (72/73)	98.4% (251/255)	98.6% (72/73)
	EBR/GZR	93.2% (NR)	95.9% (NR)	93.4% (NR)	93.2% (NR)
	SOF/LDV: • F0–F1 • F2–F3	 95.2% (80/84) 94.4% (68/72)	94.1% (32/34)	95.4% (83/87)	86.4% (19/22)
	OBV/PTV/RTV + DSV ± RBV	[redacted]	96.4%(12/24)	97.4% (NR)	98.5% (12/24)
2	G/P	[redacted]	[redacted]	[redacted]	[redacted]
	Peg-IFN + RBV	**IFN-eligible patients:** 81.5% (44/54)	-	-	-
	SOF/VEL	99.0% (99/100)	100.0% (15/15)	100.0% (15/15)	100.0% (4/4)
	SOF/RBV	96.3% (180/187)	89.7% (26/29	88.5% (69/78)	77.3% (NR)

SVR12 RATES % (n [where reported]) used in company model

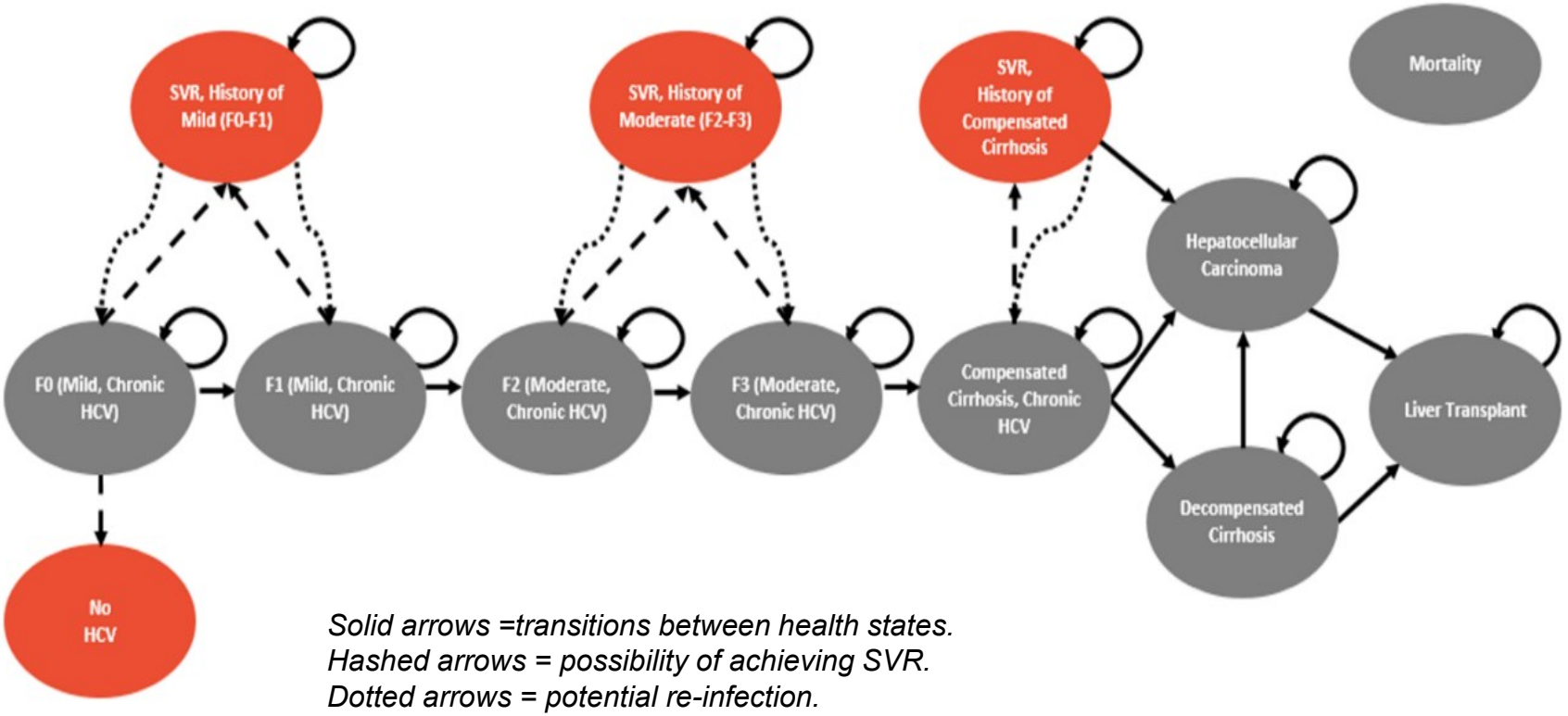
		TN		TE	
GT	Treatment	NC	CC	NC	CC
3	G/P	94.9% (149/157)	[redacted]	95.5% (21/22)	[redacted]
	SOF/VEL	98.2% (160/163)	96.7% (116/120)	91.2% (31/34)	89.9% (62/69)
	SOF+DCV	96.8% (184/190)		94.1% (32/34)	
	SOF+DCV+ RBV	-	100% (5/5)	-	100% (5/5)
	SOF + peg-IFN + RBV	-	91.3% (21/23)	NR	85.7% (30/35)
	SOF+RBV	-	77.6% (45/58)	-	59.0% (49/83
4	G/P	[redacted]	[redacted]	[redacted]	[redacted]
	SOF/VEL	100.0% (89/89)	100.0% (27/27)	100.0% (89/89)	100.0% (27/27)
	EBR/GZR	100.0% (16.71/16.71)	100.0% (1.29/1.29)	100.0% (3/3)	66.7% (4/6)
	SOF/LDV	-	100.0% (1/1)	84.6% (11/13)	100.0% (9/9)
	OBV/PTV/RTV + RBV	100.0% (42/42)	96.7% (29/30)	100.0% (49/49	98.2% (N=29)

SVR12 RATES % (n [where reported]) used in company model					
		Treatment (duration in weeks)			
		TN		TE	
GT	Treatment	NC	CC	NC	CC
5	G/P	[redacted]	[redacted]	[redacted]	[redacted]
	SOF/VEL	96.6% (28/29)	100.0% (5/5)	100.0% (11/11)	100.0% (11/11)
	SOF + peg-IFN + RBV	-	50% (1/2)	-	50% (1/2)
6	G/P	[redacted]	[redacted]	[redacted]	[redacted]
	SOF/VEL	100.0% (35/35)	100.0% (6/6	100.0% (35/35)	100.0% (6/6)
	SOF + peg-IFN + RBV	-	50% (1/2)	-	50% (1/2)

Cost-effectiveness evidence

Model structure

- Cohort Markov state-transition model (structure in line with those submitted in TA364 and TA413)
- Distinguishes between NC/CC (NC patients are further subdivided into fibrosis severity)
- Lifetime horizon with annual cycle length
- Assumes no onward HCV transmission
- Utilities from Wright et al (same source as TA430)



Solid arrows =transitions between health states.
Hashed arrows = possibility of achieving SVR.
Dotted arrows = potential re-infection.

Model inputs – transition probabilities (I)

Variable	Source	TA430 source	ERG comments
SVR12 rates	Company trials and naïve indirect comparison (see slides 16-18)	Same SVR12 rates for comparator technologies	See slide 13 for ERG critique
Fibrosis progression	GT1: Thein et al. (2008) GT2 – GT6: GT-specific multipliers from Kanwal et al. (2014) applied to rates for GT1 to account for faster progression	Did not distinguish between different non-cirrhotic fibrosis health states, and transition probabilities from fibrosis to CC were calculated from Kanwal et al. (2014)	NICE TA253 and TA364 used Thein et al. (2008). ERG explored alternative transition probabilities in its scenario analysis from Grischenko et al. (2009). **This had no impact on the results.**
Non fibrosis progression			
CC to HCC (SVR with history of CC)	Cardoso et al. (2010)	Same	-
CC to DCC	Fattovich et al. (1997)	Cardoso et al. (2010)	Fattovich et al. (1997) has been accepted by committee as being generalisable to the UK in previous NICE TA guidance.
CC to HCC (GT1)			
DCC to HCC (GT1)			
CC to HCC (GT2 – GT6)	GT-specific multipliers from Kanwal et al. (2014) applied to rates for GT1	Not applied	-
DCC to HCC (GT2 – GT6)	Same as CC to HCC	Not applied	-

Key: SVR; sustained virologic response, CC; compensated cirrhosis, DCC; decompensated cirrhosis, HCC; hepatocellular carcinoma

Model inputs - transition probabilities (II)

Variable	Source	TA430 source	ERG comments
Liver transplantation			
DCC to LT (1st year)	Siebert et al. (2003)	Siebert et al. (2005)	-
HCC to LT (1st year)		Transition not allowed in model	-
Liver mortality			
DCC to liver death	Fattovich et al. (1997)	EAP data (EASL 2016)	In TA430, a single transition probability for liver transplant to death was used from Bennett et al. which is higher than those used in this model. However, the value used in this model is consistent with TA365 and TA364
LT (1st year) to liver death	Grieve et al. (2006)	Bennett et al. (1997)	
LT (subsequent year) to liver death	Bennett et al. (1997)	Same	
HCC to liver death	Fattovich et al. (1997)	Same	
DCC to HCC (GT1)	Fattovich et al. (1997)	Cardoso et al. (2010)	

Key: SVR; sustained virologic response, CC; compensated cirrhosis, DCC; decompensated cirrhosis, HCC; hepatocellular carcinoma, LT; liver transplant

Model inputs – HRQoL

Health state	Utility values	Source
No cirrhosis - F0	0.77	Wright et al. 2006 *(used in previous Hep C appraisals)*
No cirrhosis - F1	0.77	
No cirrhosis - F2	0.66	
No cirrhosis - F3	0.66	
Compensated cirrhosis - F4	0.55	
Decompensated cirrhosis, hepatocellular carcinoma and liver transplant (1st year)	0.45	(Ratcliffe et al. 2002, used in the model by Wright et al. 2006)
Liver transplant (subsequent years)	0.67	*(used in previous Hep C appraisals)*
Source: table 82 company submission		

- Did not use utility values collected in the trials in the base-case due to small UK patient numbers.
- Utility increment after SVR: 0.05 from Wright et al. 2006
- Treatment-related utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events.
  - For comparator treatments, these (dis)utilities were derived from previous NICE submissions.
- Separate utility decrements not applied for each adverse event to avoid double counting

ERG comments on HRQoL

- Using utility values from the literature is consistent with other Hep C appraisals
  - However it is questionable whether the values from Wright et al. is relevant to UK practice in this DAA era.
  - The difference in utility of a health state with or without SVR ranges from 0.025 to 0.029 using trial data, substantially lower than the increment of 0.05 from the literature.
  - The ERG considered the effect of applying no gain in utility after SVR in its exploratory analysis but this had no impact on the cost-effectiveness of G/P.
- The impact of receiving treatment on HRQoL was taken into account in the company model using utility increments and decrements. Changes in utility for treatment related HRQoL were only applied to patients on treatment and not throughout the model time horizon.
  - ERG agreed with this approach because it takes into account both the impact of a quick response to treatment and the impact of adverse events. However for most estimates, values were based on the same studies used in the company's naïve indirect comparison which included studies with very small patient numbers.
  - the ERG explored no treatment specific health utility changes in its scenario analyses. The results showed that it had no impact on the cost-effectiveness of G/P.
- No age based utility decrements were applied
  - The ERG applied age based utility decrements derived from Ara and Brazier (2010) in the base-case. The addition of these age based utility decrements had no impact on cost-effectiveness of G/P.

Model inputs – Resource use and costs

- Company model included costs associated with treatment, monitoring and adverse events
- Company used same data (inflated to 2017 prices) as TA430 to inform health state costs
- G/P has a confidential commercial pricing arrangement
- Confidential commercial pricing arrangements also exist for:
  - Daclatavir (TA364)
  - Ombitasvir/paritaprevir/ritonavir with or without dasabuvir – 3D and 2D (TA365)
  - Elbasvir/grazoprevir (TA413)
  - Sofosbuvir /velpatasvir (TA430)

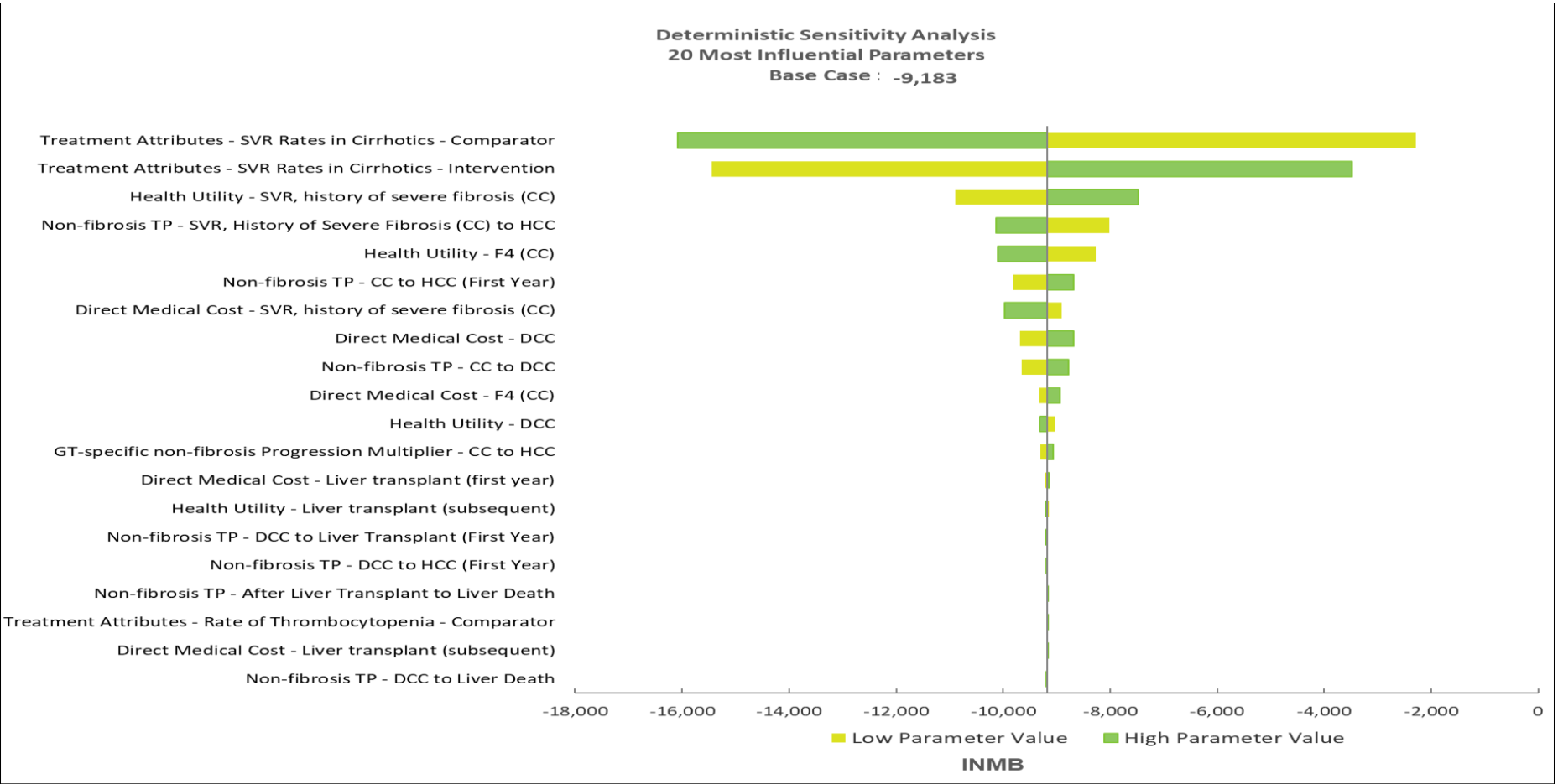
Company's base case results

- At list price, in **13** out of the 26 subgroups the ICER for G/P was lower than £20,000/QALY.
  - ICER range £2281 - £5813 per QALY gained
- In NC patients, the ICERs for G/P were all **below** £20,000/QALY except for:
  - GT2 TN IFN-eligible (£36,936/QALY)
  - GT3 TE (ICER > £167,731/QALY)
- In CC patients, the ICERs for G/P were all **above** £20,000/QALY except for:
  - GT1 TN
  - GT3 TN

Results do not include confidential commercial pricing arrangements for G/P and other comparators.

Company's deterministic sensitivity analyses

- based on the incremental net monetary benefit (INMB) of G/P against one relevant comparator for each subgroup at a threshold of £20,000 per QALY
- Showed that SVR rates had the biggest impact on the cost-effectiveness of G/P
- Example below GT3 TE CC, G/P vs. SOF/VEL:



Company's probabilistic sensitivity analyses

- The company performed probabilistic sensitivity analyses (PSA). Due to the number of subgroups (26) the company decided to compare G/P with only 1 comparator (the company chose the comparator which had the lowest incremental net monetary benefit at £20,000 per QALY gained).

G/P cost effectiveness probability (%) at £20,000 threshold (against a single comparator)

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	99.4% (SOF/LDV)	60.8% (EBR/GZR)	100% (OBV/PTV/RTV + DSV)	12.0% (SOF/VEL)
GT2	IFN-eligible: 2.4% (peg-IFN + RBV)	IFN-eligible: 43.8% (SOF/VEL)	99.8% (SOF/VEL)	37.6% (SOF/VEL)
	IFN-ineligible: 100% (SOF + RBV)	IFN-ineligible: 43.8% (SOF/VEL)		
GT3	100% (SOF/VEL)	74.0% (SOF/VEL)	0.0% (SOF + peg-IFN + RBV)	0.2% (SOF/VEL)
GT4	67.6% (OBV/PTV/RTV)	14.4% (OBV/PTV/RTV)	100% (OBV/PTV/RTV)	1.6% (OBV/PTV/RTV)
GT5	100% (SOF/VEL)	48.6% (SOF/VEL)	100% (SOF/VEL)	37.6% (SOF/VEL)
GT6	70.4% (SOF/VEL)	46.6% (SOF/VEL)	100% (SOF/VEL)	45.4% (SOF/VEL)

ERG amendment to company's PSA

- Included all comparators and modelled parameter uncertainty for SVR and AE rates in company's PSA

G/P cost effectiveness probability (%) at a willingness to pay threshold of £20,000 (difference in probability of cost-effectiveness when excluding SVR and AE rates)

Genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	**Compensated cirrhosis**	**Non-cirrhotic**	**Compensated cirrhosis**
GT1	100% (0%)	57.0% (+7%)	100% (0%)	3.4% (-6%)
GT2	IFN-eligible: 3.8% (+1%) IFN-ineligible: 100% (0%)	IFN-eligible: 56.2% (-16%) IFN-ineligible: 47.6% (+7%)	99.8% (0%)	61.2% (+24%)
GT3	100% (0%)	59.4% (-2%)	0.0% (0%)	1.0% (0%)
GT4	62.8% (-5%)	9.4% (+9%)	84.6% (-15%)	2.4% (+1%)
GT5	34.4% (-66%)	26.8% (-18%)	99.6% (0%)	20.0% (-20%)
GT6	41.2% (-29%)	46.0% (0%)	93.6% (-6%)	37.8% (-4%)

ERG exploratory analyses

The ERG's analyses had no effect on the overall cost-effectiveness of G/P. The following exploratory scenarios were conducted:

1) Changes to utility values (see slides 21-24):
   - No utility gain in SVR
   - No treatment specific health utility change
   - Age based utility decrement
2) Alternative transition probability inputs for fibrosis states (see slide 25)
3) Non-zero re-infection rates:
   - ERG used alternative probabilities for re-infection from SVR states. The re-infection probability estimate of 0.0033 from Simmons et al. (2016) was used (In the base-case re-infection probability was assumed to be zero). The addition of these re-infection probabilities had no impact on the ranking of G/P regarding cost effectiveness, total costs, and total QALYs

Innovation *(company comments)*

- 8-week regimen for all patients across all major genotypes, enabling virologic cure and cessation of treatment 4 weeks sooner than comparator DAA-based therapies.
- G/P is suitable for specific patient groups with an unmet need in the UK:
  - **Patients with GT2, GT3, GT5 or GT6 infection with chronic kidney disease (Stage 4/5)**. There are currently no licensed treatment options for these patients in the UK.
  - **Patients with genotype 3 previously treated with peg-IFN, RBV and/or SOF**. Other currently licensed treatments provide suboptimal SVR12 rates in GT3 TE patient populations; for example, the SVR12 rate for SOF/VEL in GT3 TE patients with cirrhosis is <90%.
- A positive recommendation for G/P in TN NC patients across all 6 major genotypes regardless of IFN-eligibility would remove the need for baseline resistance associated variance (RAV) and viral load testing
- favourable safety profile which suggests minimal monitoring may be required
- oral, once-daily regimen could enable treatment monitoring to continue in primary care which could help those groups who are recognised to have difficulty engaging with secondary care services. This could improve access and adherence to treatment, resulting in better treatment outcomes.

Equalities

- During the scoping process it was noted that HCV disproportionately affects certain populations such as certain immigrant populations, prison populations, and drug users, which leads to poor quality care and potential discrimination in these groups
- Any recommendations on the use of glecaprevir-pibrentasvir would be irrespective of whether or not the person is in prison, or uses injectable drugs.
- Related technology appraisals have already addressed the higher representation of minority ethnic groups in certain HCV genotypes, giving consideration to whether anything could be done to remove or reduce the disproportionate impact on the protected groups. The Committee may need to discuss similar equality issues for glecaprevir-pibrentasvir, where applicable.

Authors

- **Victoria Kelly**
  Technical Lead
- **Nwamaka Umeweni**
  Technical Adviser
- with input from the Lead Team. Gillian Ells (clinical), Simon Dixon (cost effectiveness), Rebecca Harmston (patient perspective)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Glecaprevir/pibrentasvir for treating chronic hepatitis C [ID1085]

Document A

Company evidence submission summary for committee

AbbVie Ltd confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

July 2017

File name	Version	Contains confidential information	Date
1. ID 1085 [Redacted]_GP (Maviret)_NICE Document A_FINAL_Amended CI_ 18.10.17	**1**	**No**	**18/10/2017**

Instructions for companies

This is the template you should use to summarise your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission summary must not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted. Please submit a draft summary with your main evidence submission. The NICE technical team may request changes later.

When cross referring to evidence in the main submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).

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.

Highlighting in the template (excluding the contents list)

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

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

Submission summary

A.1 Health condition

Hepatitis C virus (HCV) infection represents a severe burden on patients and healthcare systems around the world. Six major genotypes (GT 1–6) of HCV have currently been identified.[1] Within the UK, GT1 and GT3 are most prevalent, accounting for 47% and 44% of HCV infection cases, respectively.[2] Importantly, GT3 is associated with the highest risk of developing cirrhosis and hepatocellular carcinoma (HCC).[2]

Acute HCV infection is mostly asymptomatic; approximately 20–30% of patients present with clinical symptoms. The majority of individuals infected with the virus are unaware they have been infected, risking onward transmission.[3] Approximately 75–85% of patients progress to chronic hepatitis C (CHC) infection, as defined by the presence of serum HCV RNA for >6 months.[4]

CHC induces injury and inflammation of the liver, resulting in fibrosis; 10–20% of patients progress to cirrhosis over 20–30 years. It is not uncommon for patients to remain unaware they are infected with HCV until they present with complications associated with cirrhosis.[5, 6] Initially the liver is able to "compensate" for the damage caused to areas by cirrhosis.[4] Patients who "decompensate" have a 15–20% risk of death in the subsequent year.[4,5] Patients with cirrhosis due to CHC risk progressing to end-stage liver disease or developing HCC. The annual risk of patients developing HCC for patients with cirrhosis is 1–5%.[5] The principal form of long-term treatment for patients with decompensated cirrhosis (DCC) and HCC is liver transplantation.[4]

A.2 Clinical pathway of care

The aim of treatment is to achieve a sustained virologic response, meaning complete clearance of the virus and cure.

Historically, treatment for CHC consisted of peginterferon alfa, with or without ribavirin (RBV). Now, standard of care for almost all patients consists of one of a number of directly acting antiviral regimens (DAAs). For CHC patients for whom treatment does not provide successful cure and who progress to end-stage liver disease and/or HCC, the main form of treatment is liver transplantation.[4]

When considering treatment of CHC in England specifically, review of current NICE technology assessment guidance provides a summary of the treatments available as potential therapeutic options for a given CHC patient subgroup. There is no NICE clinical guideline for hepatitis C to then distinguish which of the NICE-recommended therapies might represent standard of care. This is because in January 2014 the development of a hepatitis C clinical guideline by NICE was paused until NICE technology appraisals evaluating new pharmacological therapies had been published.[7] As of September 2016, NICE has decided that the development of this guideline should remain paused until there is stability in the availability of treatments and the cost to the NHS of pharmacological therapies for this condition.[7]

Table 1 presents a matrix of NICE-recommended therapies organised by genotype, cirrhosis status and treatment history. Currently, the only DAA regimen without interferon (IFN) and/or RBV that has a recommendation in all 6 genotype populations of HCV infection is sofosbuvir/velpatasvir (SOF/VEL, brand name Epclusa®). However, in GT2 SOF/VEL is only recommended for treatment-naïve (TN) non-cirrhotic (NC) patients who cannot tolerate IFN-

based treatments. Although Table 1 presents a comprehensive overview of all therapies with NICE recommendations, current clinical practice may constitute a more restricted number of therapies within each patient subgroup. Indeed, therapies highlighted in *grey italics* represent therapies that, although associated with a positive NICE recommendation for use in the NHS, no longer form part of current clinical practice. This is based on clinical expert opinion as well as review of the treatment options specified in the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1) which also includes a NHS England determined 'rate card'. The 'rate card' is an NHSE term used to describe therapies which were awarded contracts with NHSE based on the tender outcomes.[3] The 'rate card' also assigns a sequence of use, *i.e.* specifies first, second and third line treatments and there is a CQUIN (Commissioning for Quality and Innovation payments framework) which incentivises the alignment of specialist led multidisciplinary team (MDT) decisions with NHS England published rate cards. It is therefore reasonable to assume that only therapies listed on the rate card will be used within NHS England and comprise current clinical practice.

As described in Section A.16 (Innovation), in the context of the current treatment landscape described above G/P has the potential to simplify the clinical pathway of care in HCV by providing a well-tolerated, once-daily, oral treatment with a short (8 week) treatment duration in a large proportion of patients with HCV (i.e. TN NC patients), an anticipated pan-genotypic marketing authorisation, no requirement for baseline resistance-associated variant (RAV) and viral load testing in patient groups within the anticipated licence, and the potential to remove the requirement for genotyping to make treatment decisions. G/P addresses an unmet need for HCV therapy in several specific CHC patient populations, as recognised by its Promising Innovative Medicine (PIM) status and Early Access to Medicines Scheme (EAMS) designation, including patients with severe renal impairment and specific treatment-experienced (TE) GT3 patients. Finally, in recognition of the fact that the cost of HCV treatment has a relatively high budget impact, the manufacturer has undertaken to introduce a confidential pricing agreement with NHSE's commissioning medicines unit (CMU).

Table 1. Matrix of NICE-recommended therapies for CHC

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	C	NC	C
1	• SOF/VEL (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (24/48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • SOF/LDV (8) • OBV/PTV/RTV + DSV (12), 1a: + RBV • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (24), or peg-IFN + RBV (4) then BOC + peg-IFN + RBV (32) then peg-IFN + RBV (12)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (12), or TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) **Treatments only recommended for patients with significant fibrosis[c]:** • SOF + DCV (12)	• SOF/VEL[+] (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (24/48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • *SOF/LDV (12) • *OBV/PTV/RTV + DSV + RBV (12), 1a: (24)[b] • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • *SOF + DCV ± RBV (24)	• SOF/VEL (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • SOF/LDV (12) • OBV/PTV/RTV + DSV (12), 1a: + RBV • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (32) then peg-IFN + RBV (12), or peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (12), or TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) **Treatments only recommended for patients with significant fibrosis[c]:** • SOF + DCV (12)	• SOF/VEL[+] (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • *SOF/LDV[a] (12) • *OBV/PTV/RTV + DSV + RBV (12), 1a: (24)[b] • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • *SOF + DCV ± RBV (24)

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	C	NC	C
2	• Peg-IFN + RBV (24) • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • SOF/VEL (12) • SOF + RBV (12)	• SOF/VEL[+] (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • SOF + RBV (12)	• SOF/VEL[+] (12) • SOF + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL[+] (12) • SOF + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)
3	• SOF/VEL (12) • Peg-IFN + RBV (24) • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:** • SOF + DCV (12)	• SOF/VEL[+] ± RBV (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • SOF + RBV (24) • *SOF + DCV + RBV (24)	• SOF/VEL (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:** • SOF + DCV (12)	• SOF/VEL[+] ± RBV (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • SOF + RBV (24) • *SOF + DCV + RBV (24)
4	• SOF/VEL (12)	• SOF/VEL[+] (12)	• SOF/VEL (12)	• SOF/VEL[+] (12)

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	C	NC	C
	• *Peg-IFN + RBV (24/48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • OBV/PTV/RTV + RBV (12) • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12)* • Best supportive care (watchful waiting) **Treatments only recommended for patients with significant fibrosis[c]:** • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* **Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:** • *SOF + DCV (12)*	• *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (24/48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • *SOF/LDV (12) • OBV/PTV/RTV + RBV (24)[b] • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12)* • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • **SOF + DCV ± RBV (24)*	• *Peg-IFN + RBV (48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • SOF/LDV (12) • OBV/PTV/RTV + RBV (12) • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12/36)* • Best supportive care (watchful waiting) **Treatments only recommended for patients with significant fibrosis[c]:** • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* **Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:** • *SOF + DCV (12)*	• *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • *SOF/LDV[a] (12) • OBV/PTV/RTV + RBV (24)[b] • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12/36)* • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • **SOF + DCV ± RBV (24)*
5 or 6	• SOF/VEL (12)	• SOF/VEL[+] (12)	• SOF/VEL (12)	• SOF/VEL[+] (12)

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	C	NC	C
	• *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)

*CC only (i.e. not recommended for DCC)
[+] + RBV if DCC
[a]Recommended only if all the following criteria are met: Child-Pugh class A, platelet count of 75,000/mm^3 or more, no features of portal hypertension, no history of HCV-associated decompensation episode and not previously treated with an NS5A inhibitor; [b]TA365 for OBV/PTV/RTV ± DSV was published before the results from TURQUOISE-III and AGATE-I became available and the NICE recommendation therefore stipulates the use of OBV/PTV/RTV ± DSV with RBV for GT1b patients with CC, and OBV/PTV/RTV + RBV for GT4 CC patients for 24 weeks. Subsequently, TURQUOISE-III demonstrated the efficacy of treatment with OBV/PTV/RTV + DSV for 12 weeks without RBV in GT1b patients with CC,[9] and AGATE-I demonstrated the efficacy of OBV/PTV/RTV + RBV for 12 weeks in GT4 patients with CC.[10] The licence for OBV/PTV/RTV ± DSV now reflects this. Therefore OBV/PTV/RTV + DSV without RBV for 12 weeks is used as the comparator in the economic analysis of this submission for GT1b patients with CC, and OBV/PTV/RTV + RBV for 24 weeks is used for GT4 CC patients; [c]Significant fibrosis is defined as METAVIR fibrosis stage F3 and F4.
Abbreviations: BOC, boceprevir; C, cirrhotic; CC, compensated cirrhosis; DCC, decompensated cirrhosis; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; peg-IFN, pegylated-IFN; PTV, paritaprevir; RAV, resistance associated variant; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; TN, treatment-naïve; TE, treatment-experienced; VEL, velpatasvir
Therapies highlighted in *grey italics* represent therapies that, although associated with a positive NICE recommendation for use in the NHS, no longer form part of current clinical practice and are therefore not considered as comparators to G/P in this submission

A.3 Equality considerations

The use of glecaprevir/pibrentasvir (G/P) is not expected to raise any equality issues in current treatment practice. As a pan-genotypic regimen, a recommendation for the use of G/P across the major HCV genotypes may contribute to a reduction in equality concerns by providing access to the same DAA for all patients regardless of genotype, where genotype may be correlated with protected characteristics.

G/P is a simple, once-daily, oral regimen with a short treatment duration across all 6 major genotypes in TN NC patients, no requirement for baseline RAV or viral load testing in patient groups within the anticipated licence, and the potential for minimal monitoring. Furthermore, if G/P achieves a positive recommendation in all TN NC subgroups regardless of genotype and IFN-eligibility, all patients in this subgroup within the anticipated licence for G/P would be eligible for an 8-week treatment course of G/P. This therefore has the potential to remove the requirement to genotype any TN NC patients, who represent the majority of patients with HCV,[11] in order to select a NICE-recommended treatment. Taking the above into account, the introduction of G/P may reduce equality issues by providing an opportunity to increasingly provide treatment in community settings (see point 3 in Innovation Section A.16) alongside outreach services, improving access to patient populations who have difficulty engaging with secondary care services and adhering to the course of treatment.[12]

Furthermore, despite the recommendation of SOF/VEL by NICE across genotypes 1-6 there remains some unmet needs that SOF/VEL does not address. In the GT3 population, G/P presents a significant advantage over SOF/VEL for GT3 TN NC patients due to the availability of an 8-week treatment duration. This is of particular importance as GT3 is one of the most prevalent genotypes in the UK and is the predominant strain of infection in South Asian populations, who carry a disproportionately large burden of HCV infection in North Wales and England.[13-15]

In addition, SOF/VEL is not recommended by NICE for the treatment of GT2 TN NC patients who are eligible for treatment with IFN. The only therapy available to this subgroup of patients is 24 weeks of peg-IFN + RBV. IFN- and RBV-based antiviral treatments are associated with significant side-effects that negatively impact quality of life.[16] G/P offers GT2 TN NC IFN-eligible patients an IFN- and RBV-free treatment option with a substantially shorter treatment duration (8 weeks), providing an opportunity reduce inequalities in access to DAA-based regimens with a short treatment duration in this patient population

A.4 The technology

Table 2 Technology being appraised – B.1.2 (page 23)

UK approved name and brand name	Glecaprevir/pibrentasvir (Maviret®); referred to in this submission as G/P
Mechanism of action	G/P comprises a combination of two DAAs that have individual mechanisms of action against HCV: glecaprevir (ABT-493) inhibits the NS3/4A protease whilst pibrentasvir (ABT-530) inhibits the NS5A protein. As a result, G/P interferes with multiple, key steps in the viral lifecycle.

<table>
<tr><td></td><td>The NS3/4A protease is a heterodimer complex of NS3 and NS4A proteins, whereby NS3 contains a serine protease domain and the central region of NS4A functions as a cofactor for protease activity.[17, 18] The protease is responsible for catalysing the breakdown of the HCV encoded polyprotein into NS3, NS4A, NS4B, NS5A and NS5B non-structural (NS) proteins, which are required for viral replication.[17] Glecaprevir blocks the activity of the NS3/4A protease, and so impairs HCV replication.[19]

The NS5A protein plays a crucial role in HCV replication, and is also involved in the assembly and release of virions into the surrounding extracellular fluid.[17] The protein has three domains: domains I and II take part in RNA replication, whereas domain III is integral for the assembly of HCV particles.[17] Pibrentasvir, as an NS5A inhibitor, causes conformational changes in the NS5A protein upon binding, which prevents it from interacting with other proteins in the viral membrane and host cell. As a result, HCV is left unable to form the replicase complex, and so cannot replicate its RNA.[17, 20]</td></tr>
<tr><td>Marketing authorisation/CE mark status</td><td>G/P (Maviret®) was reviewed under the EMA's accelerated assessment program, with a CHMP positive opinion adoption at Day-120 of the procedure. Full marketing authorisation is currently anticipated by late July or early August.
G/P is currently available to patients meeting certain clinical criteria in the UK via an Early Access to Medicines Scheme.[21]</td></tr>
<tr><td>Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC)</td><td>On June 22, 2017, the CHMP adopted a positive opinion, recommending the granting of marketing authorisation for Maviret®. The therapeutic indication for Maviret® is the treatment of chronic hepatitis C virus (HCV) infection in adults.</td></tr>
<tr><td>Method of administration and dosage</td><td>Oral administration of 100 mg / 40 mg film-coated tablets.
Three tablets taken together once daily (300 mg / 120 mg OD), with food, for 8 weeks, 12 weeks or 16 weeks as shown in Table 3.
Table 3: Treatment duration for anticipated licence
<table>
<tr><th>Patient population</th><th>NC</th><th>CC</th></tr>
<tr><td>TN</td><td>8 weeks for all genotypes</td><td>12 weeks for all genotypes</td></tr>
<tr><td>TE, previously treated with:
• Peg-IFN + RBV
• SOF + peg-IFN + RBV
• SOF + RBV</td><td>GT1,2, 4–6: 8 weeks

GT3: 16 weeks</td><td>GT1, 2, 4–6: 12 weeks

GT3: 16 weeks</td></tr>
</table>
Abbreviations: CC, compensated cirrhosis; GT, genotype; NC, non-cirrhotic; peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve</td></tr>
<tr><td>Additional tests or investigations</td><td>No additional tests or investigations beyond those that are already standard practice for diagnosis of CHC are required.</td></tr>
<tr><td>List price and</td><td>The list price per pack is £12,993.66. List price for treatment would therefore be £25,987.32 for 8 weeks of treatment, £38,980.98 for 12 weeks of treatment, and</td></tr>
</table>

average cost of a course of treatment	£51,974.64 for 16 weeks of treatment.
Patient access scheme (if applicable)	The company is negotiating a pricing agreement with the CMU such that the total regimen cost of G/P is [redacted]. This is pending acceptance at the time of submission. This is not a PAS but represents a negotiated confidential pricing agreement.

Abbreviations: CHC, chronic hepatitis C; CHMP, Committee for Medicinal Products for Human Use; CMU, Commercial Medicines Unit; DAA, directly-acting antiviral; EMA, European Medicines Agency; G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; NS, non-structural; OD, once daily; RNA, ribonucleic acid; PAS, patient access scheme; SmPC, Summary of Product Characteristics; SVR, sustained virologic response

A.5 Decision problem and NICE reference case

The submission covers the technology's full marketing authorisation for this indication.

The company submission is for the most part consistent with the final NICE scope and the NICE reference case. Some comparators and subgroups described in the final NICE scope were excluded. Comparators that no longer represent current clinical practice, in line with expert clinical opinion and the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1), were not considered in the company submission.[8] The submission already considers an extensive number of subgroups subdivided by genotype, treatment history and cirrhosis status. Further subgroup analyses were therefore not performed, in order to focus the decision problem on the subgroups defined by genotype, treatment history and cirrhosis status around which NICE treatment recommendations are based.

Table 4. The decision problem – B.1.1 (page 20)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with CHC: • who have not had treatment for CHC before (TN) • who have had treatment for CHC before (TE)	Per final scope	N/A
Intervention	Glecaprevir/pibrentasvir; referred to in this submission as G/P	Per final scope	N/A
Comparator(s)	• Best supportive care (no active pharmacological treatment) (GT1-6) • DCV in combination with SOF, with or without RBV (for specific people with GT1, GT3 or GT4; as recommended by NICE) • EBR/GZR (for GT1 or GT4) • SOF/LDV (for specific people with GT1 or GT4; as recommended by NICE) • OBV/PTV/RTV with or without DSV or RBV (for GT1 or GT4) • PegIFNα with RBV (for GT1– 6) • SOF in combination with RBV, with or without pegIFNα (for specific people with GT1–6; as recommended by NICE) • SOF/VEL (for specific people with	• Best supportive care (no active pharmacological treatment) (GT1–6) • DCV in combination with SOF without RBV (for GT3 only, as recommended by NICE) • EBR/GZR (for GT1 or GT4) • SOF/LDV (for specific people with GT1 or GT4; as recommended by NICE) • OBV/PTV/RTV with or without DSV or RBV (for GT1 or GT4) • PegIFNα with RBV for GT2 non-cirrhotic treatment-naïve patients only • SOF in combination with RBV, with or without pegIFNα (for specific people with GT2, GT3, GT5 and GT6, as recommended by NICE)	The following comparators were excluded as they are not used in current NHS practice: • DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE) • PegIFNα with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients) • SOF in combination with RBV, with or without pegIFNα (for specific people with GT1 and GT4; as recommended by NICE)

	GT1–6; as recommended by NICE)	• SOF/VEL (for specific people with GT1–6; as recommended by NICE)	
Outcomes	The outcome measures to be considered include: • mortality • SVR • development of resistance to treatment • adverse effects of treatment • HRQoL	Per final scope	N/A
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • genotype • co-infection with HIV • people with and without cirrhosis • previous treatment received (with or without DAA-containing regimens) • people who have received treatment before liver transplantation, and those who have received it after liver transplantation • response to previous treatment (non-response, partial response, relapsed) • people who are intolerant to or ineligible for interferon treatment • people with and without renal	Clinical evidence for these subgroups is presented where this is available. The economic analyses are stratified by genotype, cirrhosis status and previous treatment history (naïve or experienced), in line with recent prior NICE appraisals. Separate comparators for IFN-eligible and IFN-ineligible subgroups were also considered in line with NICE guidance.	Patients co-infected with HCV/HIV-1 are modelled as the same as those with HCV mono-infection. This is consistent with the approach taken in TA430.[22] The analyses split patients into TN and TE, where the TE group was defined as patients who have not adequately responded to prior IFN/RBV-based treatment with or without SOF, in line with the clinical trial programme for G/P and its anticipated licence. Separate economic subgroup analyses are not performed for TE patients stratified by previous treatment response. This is in line with the fact that neither NICE TA guidance nor the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1) provides distinct treatment recommendations on the basis of different previous treatment response.[8] Subgroup analyses were not performed in patients who had previously

	impairment		received treatment with NS3/4A- or NS5A inhibitors as G/P is currently not anticipated to be licensed in these patients. Separate economic subgroup analyses were also not performed for patients who have received a liver transplant or for patients with renal impairment. The submission already considers an extensive number of subgroups subdivided by genotype, treatment history and cirrhosis status. Further subgroup analyses were therefore not performed, in order to focus the decision problem on the subgroups defined by genotype, treatment experience and cirrhosis status around which NICE treatment recommendations are based.
Special considerations including issues related to equity or equality	If the evidence allows, the impact of treatment on reduced onward HCV transmission will also be considered.	Onward transmission is not included in the economic model.	Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework.

Abbreviations: CHC, chronic hepatitis C; DAA, directly-acting antiviral; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GZR, grazoprevir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IFN, interferon; LDV, ledipasvir; N/A, not applicable; OBV, ombitasvir; PTV, paritaprevir; peg-IFN, pegylated IFN; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TA, technology appraisal; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

A.6 Clinical effectiveness evidence

The systematic literature review (SLR) identified 7 trials of G/P for which published literature was available, as follows:

- ENDURANCE-1
- ENDURANCE-2
- ENDURANCE-3
- ENDURANCE-4
- EXPEDITION-1
- SURVEYOR-I
- SURVEYOR-II

In addition, information on 4 further clinical trials of G/P conducted in special patient populations are included in this submission (EXPEDITION-2, EXPEDITION-4, MAGELLAN-I and MAGELLAN-II). These studies have been published, but were not identified by the SLR as trials in special populations were excluded under the SLR eligibility criteria (see Document B Appendix D).

The G/P registrational programme included a broad NC and compensated cirrhotic (CC) patient population across all major genotypes using the dose of 300 mg/120 mg. TN patients and patients with previous experience with any combination of pegylated interferon (peg-IFN), RBV, sofosbuvir (SOF), NS5A inhibitors, or PIs were permitted to enrol in the clinical trial programme, with specific inclusion criteria varied between the individual studies (see below for details). In addition, studies within the programme enrolled patients with HIV co-infection and patients with advanced renal disease (chronic kidney disease [CKD] Stage 4/5).

Table 5 describes the treatment duration for the **anticipated** licence for G/P. In the sections that follow (both efficacy and safety), the entire G/P registrational programme is described (not limited to those trials in which patients were treated in line with the anticipated licence) to demonstrate the consistency of treatment effect with G/P.

Table 5: Treatment duration for anticipated licence (not yet confirmed)

Patient population	NC	CC
TN	8 weeks for all genotypes	12 weeks for all genotypes
TE, previously treated with: • Peg-IFN + RBV • SOF + peg-IFN + RBV • SOF + RBV	GT1,2, 4–6: 8 weeks GT3: 16 weeks	GT1, 2, 4–6: 12 weeks GT3: 16 weeks

Abbreviations: CC, compensated cirrhosis; GT, genotype; NC, non-cirrhotic; peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve

Studies in TN NC patients explored 8- and 12-week treatment durations. Among GT1-, GT2-, and GT3-infected NC patients, efficacy comparisons between 8- and 12-week durations were performed through non-inferiority analyses (either between study arms or against a fixed sustained virologic response [SVR] threshold based on historical data). The programme included

one registrational study with an active-controlled design for GT3 using SOF + daclatasvir (DCV). Among GT4-, GT5-, and GT6-infected NC patients, descriptive statistical efficacy comparisons between durations were performed given the lower prevalence and thus smaller sample sizes for these genotypes. The programme also included a placebo-controlled design in one registrational study to characterise the safety of the regimen.

Studies in CC patients were conducted using a 12-week duration of treatment across patients infected with GT1, GT2, and GT4–6 and 12- or 16-week duration in GT3-infected patients (12 weeks [TN] and 16 weeks [treatment-experienced; TE]).

NC and CC subjects who failed a previous regimen containing an NS5A inhibitor and/or an NS3/4A protease inhibitor (PI) were treated for 12 or 16 weeks in one study. Finally, patients CKD Stage 4/5 infected with any of the major genotypes were included in EXPEDITION-4 with a treatment duration of 12 weeks.

A summary of the trials providing evidence for G/P is provided in Table 6 to Table 9 below. As detailed in these tables, a number of the studies are presented to provide a comprehensive overview of the clinical evidence base for G/P but are not used to inform the economic modelling:

- ENDURANCE-2 and ENDURANCE-4 were not used to populate the economic model. The results of these large registrational Phase III studies support the consistent efficacy of G/P so it was considered relevant to present these as supporting studies. These studies were not included in the economic model because the treatment duration does not align with the **anticipated** licence.

- SURVEYOR-I, Part 2 was not used to populate the economic model. The results of this study are presented as a supporting early Phase II study within the clinical development programme. This study was not included in the economic model because results for larger studies that also align with the **anticipated** licence were available

- EXPEDITION-4, MAGELLAN-I, Part 1, MAGELLAN-I, Part 2, EXPEDITION-2 and MAGELLAN-II were not used to populate the economic model. The results of these studies present the efficacy results of G/P in specific patient subpopulations. These studies were not included in the economic model because it is not considered relevant to perform separate economic analyses in these specific subpopulations. Furthermore, the subpopulation in MAGELLAN-I is not in line with the anticipated licence for G/P. For EXPEDITION-2 and MAGELLAN-II, only limited details in presented in the submission as these trials have only recent been completed.

Table 6: Clinical effectiveness evidence: ENDURANCE trials

Study	M13-590 (ENDURANCE-1)[23-25]	M15-464 (ENDURANCE-2)[26-28]	M13-594 (ENDURANCE-3)[29-31]	M13-583 (ENDURANCE-4)[32-34]
Study design	Multicentre, randomised, open-label, Phase III	Multicentre, randomised, double-blind, placebo-controlled, Phase III	Multicentre, randomised, open-label, active-controlled, Phase III	Multicentre, open-label, single-arm, Phase III
Population	• GT1 • TN or TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN (TE-PRS) • NC • With or without HIV-1 co-infection	• GT2 • TN or TE-PRS • NC	• GT3 • TN • NC	• GT4, GT5 or GT6 • TN or TE-PRS • NC
Intervention(s)	G/P (300 mg/120 mg OD) for 8 or 12 weeks	G/P (300 mg/120 mg OD) for 12 weeks	G/P (300 mg/120 mg OD) for 8 or 12 weeks	G/P (300 mg/120 mg OD) for: 12 weeks
Comparator(s)	None	Placebo	SOF + DCV for 12 weeks	None
Indicate if trial supports application for marketing authorisation	Yes	No	Yes	No
Indicate if trial used in the economic model	Yes	No	Yes	No
Rationale for use/non-use in the model	Key data for GT1 TN and TE NC patients treated with G/P for 8 weeks with the licensed dose	Treatment duration not in line with anticipated licence for NC patients	Key data for GT3 TN NC patients treated with G/P for 8 weeks with the licensed dose	Treatment duration not in line with anticipated licence for NC patients
Reported outcomes specified in the decision problem	• Mortality • **SVR**	• Mortality • SVR	• Mortality • **SVR**	• Mortality • **SVR**

Study	M13-590 (ENDURANCE-1)[23-25]	M15-464 (ENDURANCE-2)[26-28]	M13-594 (ENDURANCE-3)[29-31]	M13-583 (ENDURANCE-4)[32-34]
	• Development of resistance to treatment • **AEs** • **HRQoL**	• Development of resistance to treatment • AEs • HRQoL	• Development of resistance to treatment • **AEs** • **HRQoL**	• Development of resistance to treatment • **AEs** • **HRQoL**
All other reported outcomes	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics

Abbreviations: AE, adverse event; DCV, daclatasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IFN, interferon; LLOQ, lower limit of quantitation; NC, non-cirrhotic; OD, once daily; Peg-IFN, pegylated IFN; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-PRS, TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

Table 7: Clinical effectiveness evidence: EXPEDITION-1 and SURVEYOR-II, Parts 2 and 3

Study	M14-172 (EXPEDITION-1)[35, 36]	M14-868 (SURVEYOR-II, Part 2)[37-43]	M14-868 (SURVEYOR-II, Part 3)[38, 42-44]
Study design	Multicentre, open-label, single-arm, Phase III	Multicentre, partially-randomised open-label, Phase II	
Population	• GT1, GT2, GT4, GT5 or GT6 • TN or TE-PRS	• GT2, GT3 • TN or TE with regimens containing peg-IFN/RBV (TE-PR)	• GT3 • TN CC

Study	M14-172 (EXPEDITION-1)[35, 36]	M14-868 (SURVEYOR-II, Part 2)[37-43]	M14-868 (SURVEYOR-II, Part 3)[38, 42-44]
	• CC	• NC or CC (GT3 CC were TN only[a]; GT2 were NC only)	• TE-PRS NC CC
Intervention(s)	G/P (300 mg/120 mg OD) for 12 weeks	G/P (300 mg/120 mg OD) for 8 or 12 weeks ± RBV	G/P (300 mg/120 mg OD) for 12 or 16 weeks
Comparator(s)	None		
Indicate if trial supports application for marketing authorisation	Yes	Yes	No
Indicate if trial used in the economic model	Yes	Yes, pooled with data from the same subpopulation of patients and treatment dose and duration from Part 3	Yes For GT3 TN and TE CC, pooled with data from the same subpopulation of patients and treatment dose and duration from Part 2
Rationale for use/non-use in the model	Key data for GT1, GT2, GT4, GT5 and GT6 TN and TE CC patients treated with G/P for 12 weeks with the licensed dose	Key data for GT3 TN CC patients treated with G/P for 12 weeks with the licensed dose, and GT3 TE CC patients treated with G/P for 16 weeks with the licensed dose	Key data for GT3 TN CC patients treated with G/P for 12 weeks with the licensed dose, and GT3 TN and TE NC patients treated with G/P for 16 weeks with the licensed dose
Reported outcomes specified in the decision problem	• Mortality • **SVR** • Development of resistance to treatment • **AEs** • **HRQoL**	• Mortality • **SVR** • Development of resistance to treatment • **AEs** • **HRQoL**	• Mortality • **SVR** • Development of resistance to treatment • **AEs** • **HRQoL**
All other reported outcomes	• On-treatment virologic failure	• On-treatment virologic failure	• On-treatment virologic failure

Study	M14-172 (EXPEDITION-1)[35, 36]	M14-868 (SURVEYOR-II, Part 2)[37-43]	M14-868 (SURVEYOR-II, Part 3)[38, 42-44]
	• Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics

[a]When SURVEYOR-II, Part 2 enrolment was initiated, both TN and TE-PR GT3-infected CC patients were eligible for enrolment, but after 7 GT3 TE-PR CC patients were enrolled, enrolment was halted for these patients based on feedback from the United States Food and Drug Administration.
Abbreviations: AE, adverse event; CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HRQoL, health-related quality of life; IFN; interferon; LLOQ, lower limit of quantitation; NC, non-cirrhotic; OD, once daily; peg-IFN, pegylated IFN; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-PR, TE with regimens containing peg-IFN/RBV; TE-PRS, TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

Table 8: Clinical effectiveness evidence: SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 trials

Study	M14-867 (SURVEYOR-I, Part 2)[39, 41, 45-47]	M14-868 (SURVEYOR-II, Part 1)[38, 39, 42, 43, 48]	M14-868 (SURVEYOR-II, Part 4)[38, 42, 43, 49]
Study design	Multicentre, open-label, Phase II	Multicentre, randomised, open-label, Phase II	Multicentre, open-label, single-arm, Phase II
Population	• GT1, GT4, GT5 or GT6 • TN or TE-PR • GT1 NC and CC; GT4, GT5 and GT6 NC only	• GT2, GT3 • TN or TE-PR • NC	• GT2, GT4, GT5 or GT6 • TN or TE-PRS • NC
Intervention(s)	G/P (300 mg/120 mg OD) for 8 or 12 weeks	G/P (300 mg/120 mg OD or 200mg/120 mg OD) for 12 weeks ± RBV	G/P (300 mg/120 mg OD) for 8 weeks
Comparator(s)	None		
Indicate if trial supports application for marketing authorisation	No	No	Yes

Study	M14-867 (SURVEYOR-I, Part 2)[39, 41, 45-47]	M14-868 (SURVEYOR-II, Part 1)[38, 39, 42, 43, 48]	M14-868 (SURVEYOR-II, Part 4)[38, 42, 43, 49]
Indicate if trial used in the economic model	No	Yes, pooled with data from the same subpopulation of patients and treatment dose and duration from Part 4	Yes For GT2, pooled with data from the same subpopulation of patients and treatment dose and duration from Part 1
Rationale for use/non-use in the model	Data from larger trials were available to inform the economic model inputs for GT1 TN and TE-PR NC patients treated with G/P for 8 weeks, and from GT1 TN and TE-PR CC patients treated with G/P for 12 weeks	Key data for GT2 TN and TE NC patients treated with G/P for 8 weeks with the licensed dose	Key data for GT2, GT4, GT5 and GT6 TN and TE NC patients treated with G/P for 8 weeks with the licensed dose
Reported outcomes specified in the decision problem	• Mortality • SVR • Development of resistance to treatment • AEs • HRQoL	• Mortality • **SVR** • Development of resistance to treatment • **AEs** • **HRQoL**	• Mortality • **SVR** • Development of resistance to treatment • **AEs** • **HRQoL**
All other reported outcomes	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics

Abbreviations: AE, adverse event; CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HRQoL, health-related quality of life; IFN, interferon; LLOQ, lower limit of quantitation; NC, non-cirrhotic; peg-IFN, pegylated IFN; OD, once daily; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-PR, TE with regimens containing peg-IFN/RBV; TE-PRS, TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

Table 9: Clinical effectiveness evidence: EXPEDITION-4 and MAGELLAN-I trials

Study	M15-462 (EXPEDITION-4)[50-52]	M15-410 (MAGELLAN-I, Part 1) [53-56]	M15-410 (MAGELLAN-I, Part 2) [53, 55-58]
Study design	Multicentre, open-label, single-arm, Phase III	Multicentre, randomised, open-label, Phase II	
Population	• GT1, GT2, GT3, GT4, GT5 or GT6 • TN (all genotypes) or TE-PRS (GT1, GT2, GT4, GT5 or GT6) • NC or CC • Who had severe renal impairment or end-stage renal disease (including those on dialysis)	• GT1 • TE-DAA • NC Note that this patient population is not within the anticipated licence for G/P	• GT1, GT4, GT5 or GT6 • TE-DAA • NC or CC Note that this patient population is not within the anticipated licence for G/P
Intervention(s)	G/P (300 mg/120 mg OD) for 12 weeks	G/P (300 mg/120 mg OD) for 12 weeks ± RBV	G/P (300 mg/120 mg OD) for 12 or 16 weeks
Comparator(s)	None		
Indicate if trial supports application for marketing authorisation	No	No	Yes
Indicate if trial used in the economic model	No	No	No
Rationale for use/non-use in the model	The submission already considers an extensive number of subgroup subdivided by genotype, treatment history and cirrhosis status. A subgroup analysis for patients with severe renal impairment was therefore not performed in order to focus the decision problem on subgroups that are historically considered important in previous NICE treatment recommendations. Additionally, the patient population studied in MAGELLAN-I is not within the anticipated licence for G/P.		
Reported outcomes specified in the decision problem	• Mortality • SVR • Development of resistance to treatment	• Mortality • SVR • Development of resistance to treatment	• Mortality • SVR • Development of resistance to treatment

Study	M15-462 (EXPEDITION-4)[50-52]	M15-410 (MAGELLAN-I, Part 1) [53-56]	M15-410 (MAGELLAN-I, Part 2) [53, 55-58]
	• AEs • HRQoL	• AEs	• AEs
All other reported outcomes	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics

Abbreviations: AE, adverse event; CC, compensated cirrhosis; DAA, directly-acting antiviral; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HRQoL, health-related quality of life; IFN, interferon; LLOQ, lower limit of quantitation; NC, non-cirrhotic; peg-IFN, pegylated IFN; OD, once daily; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-DAA, TE with regimens containing DAAs; TE-PRS, TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

A.7 Key results of the clinical effectiveness evidence

A.7.1 Sustained virologic response 12 weeks after treatment (SVR12)

Overall across trials presented at licensing and summarised in this submission, G/P achieved an SVR12 rate of [redacted]%, with a virologic failure rate of [redacted]% in 2369 patients across HCV genotypes, treatment durations, and prior treatment experience, including patients with baseline polymorphisms or comorbidities (CC, renal impairment, and HIV-1 co-infection).[59]

SVR12 (intention-to-treat [ITT] population) summary

The list below is a summary of the SVR12 rates from the G/P trials described in detail in the next sections. The SVR12 rates from each trial are reported whenever possible from ITT patient subpopulations defined by genotype, treatment history and cirrhosis status (the factors upon which NICE has historically based treatment recommendations), and those highlighted in bold correspond to the (anticipated) licensed dose and treatment duration for G/P. SVR12 rates from trials in special populations (e.g. EXPEDITION-2, EXPEDITION-4, MAGELLAN-1 and MAGELLAN-2) are not included in the summary.

GT1

- TN NC
  - ENDURANCE-1[23, 25]: **G/P 8 weeks** [redacted]; G/P 12 weeks [redacted]
  - SURVEYOR-I, Part 2: **G/P 8 weeks 96.6% (28/29)**
- TN CC
  - EXPEDITION-1[36]: **G/P 12 weeks** [redacted]
- TE NC
  - ENDURANCE-1[23, 25]: **G/P 8 weeks** [redacted]; G/P 12 weeks [redacted]
  - SURVEYOR-I, Part 2: **G/P 8 weeks 100% (5/5)**
- TE CC
  - EXPEDITION-1[36]: **G/P 12 weeks** [redacted]

GT2

- TN NC
  - ENDURANCE-2*[26, 28]: G/P 12 weeks [redacted]
  - SURVEYOR-II, Part 4[38, 43, 44]: **G/P 8 weeks** [redacted]
  - SURVEYOR-II, Parts 1 and 2[37-41, 43, 48]: **G/P 8 weeks** [redacted]; G/P 12 weeks [redacted]
- TN CC
  - EXPEDITION-1[36]: **G/P 12 weeks** [redacted]
- TE NC
  - ENDURANCE-2*[26, 28]: G/P 12 weeks [redacted]
  - SURVEYOR-II, Part 4[38, 43, 44]: **G/P 8 weeks** [redacted]
  - SURVEYOR-II, Parts 1 and 2[37-41, 43, 48]: **G/P 8 weeks** [redacted]; G/P 12 weeks [redacted]
- TE CC
  - EXPEDITION-1[36]: **G/P 12 weeks** [redacted]

GT3

- TN NC
  - ENDURANCE-3[31, 60]: **G/P 8 weeks 94.9% (149/157)**; G/P 12 weeks 95.3% (222/233)
  - SURVEYOR-II, Parts 1 and 2[37-41, 43, 48]: G/P 12 weeks [redacted]

- TN CC
  - SURVEYOR-II, Part 2[37-41, 43, 48]: **G/P 12 weeks 100% (24/24**)
  - SURVEYOR-II, Part 3[43, 44]: **G/P 12 weeks 97.5% (39/40)**
- TE NC
  - SURVEYOR-II, Part 3[43, 44]: G/P 12 weeks 90.9% (20/22); **G/P 16 weeks 95.5% (21/22)**
  - SURVEYOR-II, Parts 1 and 2[37-41, 43, 48]: G/P 12 weeks [redacted]
- TE CC
  - SURVEYOR-II, Part 2[37-41, 43]: **G/P 16 weeks** [redacted]
  - SURVEYOR-II, Part 3[43, 44]: **G/P 16 weeks: 95.7% (45/47)**

GT4–6

- TN NC
  - GT4: SURVEYOR-II, Part 4[43]: **G/P 8 weeks** [redacted]
  - GT5: SURVEYOR-II, Part 4[43]: **G/P 8 weeks** [redacted]
  - GT6: SURVEYOR-II, Part 4[43]: **G/P 8 weeks** [redacted]
- TN CC
  - GT4: EXPEDITION-1[36]: **G/P 12 weeks** [redacted]
  - GT5: EXPEDITION-1[36]: **G/P 12 weeks** [redacted]
  - GT6: EXPEDITION-1[36]: **G/P 12 weeks** [redacted]
- TE NC
  - GT4–6: SURVEYOR-II, Part 4[43]: **G/P 8 weeks** [redacted]
- TE CC
  - GT4–6: EXPEDITION-1[36]: **G/P 12 weeks** [redacted]

*ITT population excluding prior SOF+ RBV ± peg-IFN failures

A.7.2 Safety

The fixed-dose combination of G/P demonstrated a favourable safety profile (see Section B.2.10) in patients treated for 8, 12, or 16 weeks, and across all populations studied. The overall safety profile was similar to that observed in patients receiving placebo or SOF + DCV. The type, frequency, and severity of AEs in CC patients were similar to those in NC patients. In addition, G/P demonstrated a favourable safety profile in patients with renal insufficiency, including patients on dialysis.

A.8 Evidence synthesis

One G/P trial included an active non-G/P comparator. This trial was conducted in GT3 TN NC patients that compared G/P to SOF + DCV (the ENDURANCE-3 study). As SOF/DCV is one of the comparators to G/P in this subgroup, this trial provides relevant direct head-to-head evidence. One trial comparing G/P to a placebo comparator was identified – the ENDURANCE-2 study in GT2 patients. However, in this study patients in the placebo arm were switched to open-label G/P after 12 weeks, and therefore this trial cannot provide a true comparison of SVR12 rates (the key outcome) for G/P versus placebo.

There are no other trials comparing G/P directly to any other comparators, and therefore an indirect treatment comparison via the SOF + DCV arm of the ENDURANCE-3 study would have been necessary to derive relative treatment effects for G/P versus other comparators. However, none of the studies identified by a clinical systematic literature review that contained a SOF/DCV arm compared SOF + DCV with any other therapies, rendering it infeasible to form a network beyond that of G/P and SOF + DCV.

In conclusion, it is not feasible to form any network between G/P and any relevant comparator therapies. Therefore, the economic model presented in Section B.3 of this submission relies on the direct use of SVR rates as reported by relevant trials of G/P and comparator therapies for the subgroup in question. AbbVie acknowledges that this approach means that the selection of SVR rates from across different trials outside of a network meta-analysis framework means that results are open to the same risks as bias as would be associated with observational studies. However, lack of control arms is a very common feature of clinical trials in hepatitis C across DAAs, with placebo-controlled comparisons considered unethical, and the infeasibility of forming a network for comparison is therefore not a feature of the G/P evidence base specifically. Indeed, in the most recent NICE appraisal of a DAA (that of SOF/VEL as part of TA430), it was acknowledged that network meta-analysis was feasible only in two subgroups. For these two subgroups, even though it was technically possible to form a network, this network was associated with such limitations as a result of trial heterogeneity that the NICE Committee agreed that it would be inappropriate for the outputs of the indirect treatment comparison to inform the cost-effectiveness model. The approach taken in this submission for G/P, although associated with limitations, is therefore consistent with the approach frequently seen in appraisals of therapies for the treatment of CHC.

A.9 Key clinical issues

- Evidence for the groups with a licensed treatment duration of 8 weeks comes from smaller trials compared to groups with a treatment duration of 12-weeks. However, these data are confirmed by non-inferiority analysis that the efficacy of G/P is maintained when the treatment duration is shortened from 12 weeks to 8 weeks, and are supported by the large body of evidence demonstrating the efficacy of the 12-week duration. Notably, a treatment duration of 8 weeks was sufficiently demonstrated to be included in the relevant subgroups of the licensed indication
- Many of the studies were designed to have an historical control rather than being randomised controlled trials (RCTs); however, this is commonplace in this disease area and many previous positive NICE appraisals have been based on such evidence
- No network meta-analysis (NMA) is possible because of the relative lack of RCT study designs in this disease area; again, this is a common feature of appraisals for hepatitis C therapies, including the recent NICE TA430

A.10 Overview of the economic analysis

A cohort Markov state-transition model was built based on previously published models of the natural history of HCV infection.[16, 61, 62] This includes a model previously developed by AbbVie for ombitasvir/paritaprevir/ritonavir ± dasabuvir (OBV/PTV/RTV ± DSV; TA365), which was assessed by NICE and received a positive recommendation.

Overall, the model therefore comprises the two key aspects of CHC: a treatment phase in which the efficacy of active treatments is captured in terms of SVR rate, and a natural history phase that simulates the lifetime disease progression of patients with HCV following treatment with anti-viral therapy depending on the outcome of the treatment phase.

The first phase of the model (‘treatment phase’) relates to the initial anti-viral treatment period, which applies data from the clinical trials to estimate the proportion of patients who achieve SVR. When running the model to generate results for CC patients, 100% of the patients entering the

'treatment' phase of the model are assumed to have CC. When running the model to generate results for NC patients, patients are stratified by fibrosis severity (F0– F3) as they enter the 'treatment' phase of the model. Distinct SVR rates are applied to NC patients compared to CC patients. No analyses were run using patients entering the first phase of the model in the DCC health state, as G/P is not licensed for use in this population.

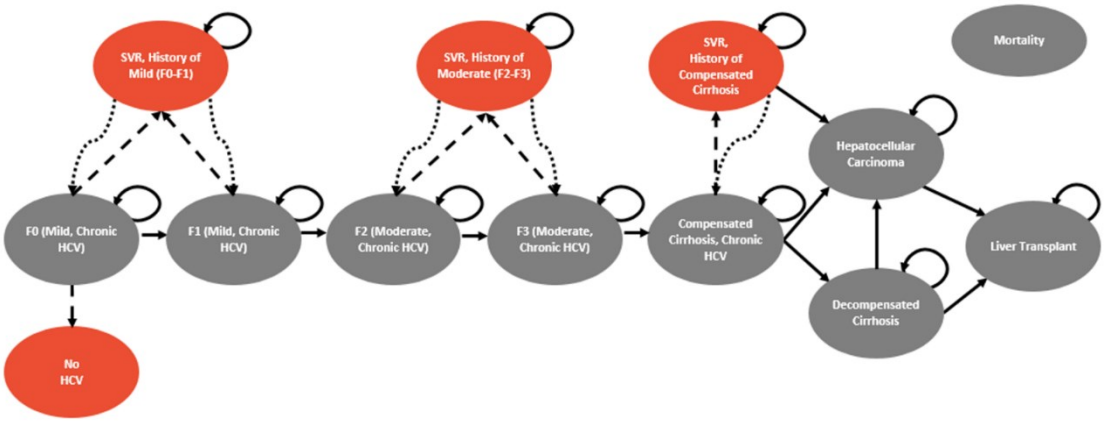
Patients then move into the 'post-treatment' natural disease progression phase of the model. This phase of the model captures long-term outcomes over the remaining life of the patient and is depicted in Figure 1. Patients enter the relevant Markov health states of this phase of the model based on the proportion of patients that have achieved SVR. Those patients that achieve SVR enter recovered health states defined by their fibrosis history (SVR, history of mild [F0–F1] fibrosis; SVR, history of moderate [F2–F3] fibrosis; SVR, history of CC [F4]); patients that do not achieve SVR remain in the grey health states in Figure 1 and have the same risk of progression to more severe disease health states (DCC, HCC, and liver transplant [LT]) as untreated patients.

Given the low probability of spontaneous clearance of HCV infection, it is assumed that spontaneous remission is not possible for patients with CHC, so the transition probability from F0 to the "no HCV" health state in Figure 1 is zero. Therefore, the only health states in the model representing recovery from CHC are the SVR states, into which patients enter with successful treatment as part of the 'treatment phase' of the model. SVR is assumed to be a permanent condition with no spontaneous reactivation of disease.

Throughout the model, patients are subject to a background risk of mortality equal to that of the general population. General mortality can occur from any Markov model health state. Additionally, patients in states representing more advanced liver disease, namely DCC, HCC or LT states, are at risk of liver-related death and therefore subject to increased risk of mortality; these states are commonly accepted as distinct stages of progressive liver disease and carry excess mortality risks.[16, 63-65]

The modelled time horizon is lifetime (70 years after starting age) and the cycle length is annual.

Figure 1: Model diagram – Post-treatment, natural disease progression phase – B.3.2 (page 142)



Note: Health states are depicted by ellipses, arrows represent permissible transitions between health states while loops represent no transition. Hashed arrows depict the possibility of achieving SVR. Dotted arrows depict a potential reinfection. Death is possible from any health state. Liver-related death is possible from DCC, HCC, and LT.

Abbreviations: DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C Virus; LT, liver transplant; SVR, sustained virologic response

Relevant comparator treatments were considered for each patient subgroup defined by genotype, cirrhosis status, prior treatment history, and, in the case of GT2 NC patients, IFN-eligibility. Comparators were determined based on consideration of NICE-approved treatments for CHC, expert advice from English clinicians, and the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1), which represent current clinical practice.[8] Treatment-experienced in the model is defined as meaning the patient has not adequately responded to prior IFN/RBV-based treatment with or without SOF in line with the clinical trial programme of G/P.

A.11 Incorporating clinical evidence into the model

The key clinical inputs in the model are the SVR rates for G/P and for comparator treatments, transition probabilities for disease progression in the absence of an SVR, adverse event rates, average treatment duration and treatment-related change in health utility.

The clinical data used for SVR rates corresponds to SVR12, defined as HCV RNA < lower limit of quantification (LLOQ) at 12 weeks after the end of treatment, and based on the intention-to-treat population for each trial. Given the lack of head-to-head trial data for G/P and comparator treatments other than SOF/VEL, and the infeasibility of forming a network for indirect treatment comparison, observed SVR12 rates from AbbVie trials and comparator trials were used directly in the model to determine the probability of patients achieving SVR following treatment. Trials were selected to provide SVR12 rates for the model based on alignment with the anticipated licence, and data from registrational trials were used preferentially. For the most part, sources of SVR data for comparator therapies were aligned to the sources used in the recent NICE appraisal of SOF/VEL (TA430), with differences described in full in Document B Section B.3.3.2.

Transition probabilities were applied for progression through stages of fibrosis, progression between CC, DCC and HCC, transitions to liver transplant health states and for liver-related death. These transition probabilities were all derived from literature sources that have been used previously in a number of cost-effectiveness analyses of therapies for the treatment of chronic HCV, including recent TA appraisals such as TA365 and TA430.[22, 66]

Finally, adverse event (AE) rates, treatment duration and treatment-related change in health utility inputs were derived from the same clinical trial sources as used to determine SVR12 rates for each intervention in each subgroup.

A.12 Key model assumptions and inputs

The sources of key model inputs about which there might be uncertainty are summarised in Table 10 below. More specific detail regarding inputs to the economic model is provided in Section B.3.3.3.

Uncertainty in SVR12 rates stems from the infeasibility of conducting any formal indirect comparison. SVR12 rate inputs are seen to be key drivers of incremental cost-effectiveness results.

Uncertainty in transition probability inputs relates to well-documented discussion in previous appraisals in CHC regarding which literature sources represent the most appropriate choices.

Given the discussion surrounding these sources in previous appraisals, the sources are documented here for transparency. However, it should be noted that in comparison to SVR12 rates, the source of transition probabilities is typically not a major influence on incremental cost-effectiveness results.

Table 10: Key model assumptions and inputs

Model input and cross reference	Source/assumption	Justification
SVR12 rates for G/P and comparators	Direct from clinical trial data, as identified by systematic literature review or AbbVie data on file.	Clinical trials provide the most robust level of evidence for determining SVR12 rates with a given therapy. As no network meta-analysis was feasible, SVR12 rates were taken directly from the clinical trial data for each relevant trial. This is consistent with prior appraisals in CHC. Specific details of the trials informing SVR inputs for each intervention and in each subgroup are provided in Document B, Section B.3.3.
Fibrosis progression transition probabilities (GT1)	Equations from Thein et al. (2008)[67] and patient characteristics from TA364[68]	Thein et al. (2008)[67] is a well-established source for fibrosis progression transition probabilities that has been used in previous appraisals in CHC.
GT-specific fibrosis progression multipliers	Kanwal et al. (2014)[69]	Kanwal et al. (2014)[69] is a well-established source for fibrosis progression transition probabilities that has been used in previous appraisals in CHC, including the recent pan-genotypic submission for SOF/VEL (TA430).[22]
Non-fibrosis disease progression	Various sources for specific transition probabilities as follows: -SVR, history of CC (F4) to HCC: Cardoso et al. (2010)[70] -Transitions between CC, HCC and DCC: Fattovich et al. (1997)[71] -DCC/HCC to liver death: Fattovich et al. (1997)[71] -LT first year to liver death: Grieve et al. (2006)[65] -LT subsequent year to liver death: Bennett et al. (1997)[72]	Literature sources consistent with those that have been used in previous appraisals of HCV therapies.
Re-infection and onward transmission (B.3.2.2.4 [page 151])	Re-infection and onward transmission are not modelled	NICE has previously concluded that without a model that incorporates both re-infection and transmission, cost-effectiveness results excluding re-infection and transmission are acceptable for decision making.[73]

Abbreviations: CC, compensated cirrhosis; CHC, chronic hepatitis C; DCC, decompensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCC, hepatocellular carcinoma; LT, liver transplant; SOF/VEL, sofosbuvir/velpatasvir; SVR, sustained virologic response

A.13 Base-case ICER (deterministic)

Base-case incremental cost-effectiveness analysis results are presented with patients stratified by genotype, treatment history and cirrhosis status. Patients are also stratified by IFN-eligibility for GT2 TN patients. Therefore in total, there are 26 separate subgroups; given the extensive number of subgroups, it is not feasible within the page limit for this summary document to provide full details of the incremental analyses in all subgroups. Therefore, the results of the base case analyses using list price for all therapies are instead summarised in Table 11. The full results can be found in Document B Section B.3.7. In considering these results it should be noted that several comparators have PAS price agreements, and a confidential pricing agreement with the commercial medicines unit (CMU) for G/P is currently under negotiation. Therefore the prices used in the base-case, and the resulting ICERs, are not a realistic representation of the cost-effectiveness of G/P.

Table 11: Summary of base-case incremental cost-effectiveness analysis results (list price)

GT	Treatment history	Cirrhosis status	Result
GT1	TN	NC	In the two GT1 NC populations, G/P is cost-effective versus no treatment with ICERs <£3,200. All other regimens are dominated. In the GT1 TN CC population, G/P has an ICER of £12,927 per QALY gained versus EBR/GZR, which has an ICER of £4,778 versus no treatment. All other regimens are dominated. In the GT1 TE CC population, G/P is dominated by SOF/VEL. SOF/VEL has an ICER of £7,928 versus EBR/GZR, which has an ICER of £5,423 versus no treatment. All other regimens are dominated
		CC	
	TE	NC	
		CC	
GT2	TN	NC	In the IFN-eligible population, G/P has an ICER of £36,936 versus peg-IFN + RBV In the IFN-ineligible population, G/P is cost-effective treatment versus no treatment (ICER of £5,620), with all other regimens either dominated or with an ICER far above the conventional cost-effectiveness threshold in the incremental analysis
		CC	In both the IFN-eligible and IFN-ineligible populations, G/P is dominated by SOF/VEL, which has an ICER of £5,243 versus no treatment in both populations. The other treatment option in the IFN-ineligible population (SOF + RBV) is extendedly dominated
	TE	NC	G/P is cost-effective versus no treatment (ICER of £5,813) with all other regimens either dominated or with an ICER far above the conventional cost-effectiveness threshold in the incremental analysis
		CC	G/P is dominated by SOF/VEL, which has an ICER of £5,561 versus no treatment. The other treatment option (SOF + RBV) is also dominated.
GT3	TN	NC	In all GT3 TN populations, G/P is cost-effective versus no treatment (ICERs <£5,200), with all other regimens either dominated or with an ICER far above the conventional cost-effectiveness threshold in the incremental analysis
		CC	
	TE	NC	G/P has an ICER of £167,731 versus SOF + peg-IFN + RBV, which has an ICER of £5,396 versus no treatment. All other

			treatments are dominated
		CC	G/P has an ICER of £92,584 versus SOF/VEL, which has an ICER of £6,537 versus no treatment. All other regimens are either dominated or have an ICER far above the conventional cost-effectiveness threshold in the incremental analysis
GT4	**TN**	**NC**	G/P is cost-effective versus no treatment (ICER of £4,039), with all other regimens either dominated or with an ICER >£20,000
		CC	G/P is dominated by SOF/VEL. OBV/PTV/RTV is cost-effective versus no treatment (ICER of £3,451). EBR/GZR has an ICER of £29,607 versus OBV/PTV/RTV, and SOF/VEL has an ICER of £373,179 versus EBR/GZR. SOF/LDV is also dominated by SOF/VEL
	TE	**NC**	G/P is cost-effective versus no treatment (ICER of £2,938), with all other regimens either dominated or with an ICER far above the conventional cost-effectiveness threshold in the incremental analysis
		CC	G/P is dominated by SOF/VEL. OBV/PTV/RTV is cost-effective versus no treatment (ICER of £3,465). SOF/VEL has an ICER of £113,791 versus OBV/PTV/RTV
GT5	**TN**	**NC**	G/P is cost-effective versus no treatment (ICER of £3,347), with SOF/VEL dominated by G/P
		CC	G/P is dominated by SOF/VEL. SOF/VEL has an ICER of £5,121 versus no treatment; SOF + peg-IFN + RBV is also dominated by SOF/VEL
	TE	**NC**	G/P is cost-effective versus no treatment (ICER of £2,938); the ICER of SOF/VEL versus G/P is far above the conventional cost-effectiveness threshold
		CC	G/P is dominated by SOF/VEL. The ICER of SOF/VEL versus no treatment is £5,398; SOF + peg-IFN + RBV is also dominated by SOF/VEL
GT6	**TN**	**NC**	G/P is cost-effective versus no treatment (ICER of £4,534) at a cost-effectiveness threshold of £20,000; the ICER of SOF/VEL versus G/P is £28,640
		CC	G/P is dominated by SOF/VEL. SOF/VEL has an ICER of £5,121 versus no treatment; SOF + peg-IFN + RBV is also dominated by SOF/VEL
	TE	**NC**	G/P is cost-effective versus no treatment (ICER of £2,938); the ICER of SOF/VEL versus G/P is far above the conventional cost-effectiveness threshold
		CC	G/P is dominated by SOF/VEL. The ICER of SOF/VEL is £5,398; SOF + peg-IFN + RBV is also dominated by SOF/VEL

Abbreviations: CC, compensated cirrhosis; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; GZR, grazoprevir; ICER, incremental cost-effectiveness ratio; IFN, interferon; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; peg-IFN, pegylated IFN; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

A.14 Probabilistic sensitivity analysis

Given the number of subgroups and the number of comparators within each subgroup, it was not feasible to run a probabilistic sensitivity analysis (PSA) for all comparisons in all patient subgroups. Therefore, for each of the 26 subgroups PSA was run for the comparison of G/P to a single comparator treatment. The comparator selected in each subgroup was the comparator against which the case for cost-effectiveness of G/P was least demonstrated. This was judged as

the comparator against which G/P had the lowest incremental net monetary benefit (INMB; issues of dominance rendered the use of ICERs inappropriate to make this judgement; hence the use of INMB) when valuing a quality-adjusted life year (QALY) at £20,000 per QALY gained. A summary of the results of the PSA in each subgroup when considering all therapies at list price is provided in Table 12.

Table 12: PSA results

Genotype	Treatment history	Cirrhosis status	Comparator	Probability of cost-effectiveness of G/P at WTP £20,000	Probability of cost-effectiveness of G/P at WTP £30,000
GT1	TN	NC	SOF/LDV	99.4%	99.2%
		CC	EBR/GZR	57.0%	67.4%
	TE	NC	OBV/PTV/RTV + DSV	100.0%	100.0%
		CC	SOF/VEL	12.0%	12.4%
GT2	TN	NC	IFN-eligible: peg-IFN + RBV	0.4%	18.4%
			IFN-ineligible: SOF + RBV	100.0%	100.0%
		CC	IFN-eligible:* SOF/VEL	41.0%	42.4%
			IFN-ineligible:* SOF/VEL	41.0%	42.4%
	TE	NC	SOF/VEL	100.0%	96.8%
		CC	SOF/VEL	38.8%	43.0%
GT3	TN	NC	SOF/VEL	100.0%	99.6%
		CC	SOF/VEL	73.8%	73.2%
	TE	NC	SOF + peg-IFN + RBV	0.0%	0.0%
		CC	SOF/VEL	0.2%	3.4%
GT4	TN	NC	OBV/PTV/RTV	78.6%	52.8%
		CC	OBV/PTV/RTV	12.6%	22.4%
	TE	NC	OBV/PTV/RTV	100.0%	100.0%
		CC	OBV/PTV/RTV	2.4%	6.0%
GT5	TN	NC	SOF/VEL	100.0%	100.0%
		CC	SOF/VEL	47.4%	48.0%
	TE	NC	SOF/VEL	100.0%	100.0%
		CC	SOF/VEL	46.4%	48.6%
GT6	TN	NC	SOF/VEL	74.4%	57.8%
		CC	SOF/VEL	48.6%	49.4%
	TE	NC	SOF/VEL	100.0%	100.0%
		CC	SOF/VEL	46.6%	46.8%

*Note: In GT2 TN CC, the comparator for PSA in the IFN-eligible and IFN-ineligible populations is the same (SOF/VEL). There were no differences in modelling of the IFN-eligible vs IFN-ineligible subgroups (i.e. no differences in model inputs), with the only difference between these subgroups being the comparator list for the incremental analysis. Therefore, when performing analysis in the IFN-eligible vs IFN-ineligible subgroups using the same

comparator, the results are identical.
Abbreviations: CC, compensated cirrhosis; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; PSA, probabilistic sensitivity analysis; PTV, paritaprevir; peg-IFN, pegylated IFN; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir; WTP, willingness-to-pay threshold

A.15 Key sensitivity and scenario analyses

Deterministic sensitivity analysis (DSA)

As per the PSA (see above), in the interests of pragmatism given the number of subgroups and comparators within subgroups, DSA was conducted for the comparison of G/P and a single comparator in each subgroup. In the vast majority of subgroups, the SVR rate for G/P or the SVR rate for the comparator were found to be the key model drivers influencing results of the cost-effectiveness analysis.

Scenario analysis

Two scenario analyses were conducted:

1. A pricing scenario analysis in which the cost for G/P was adjusted in line with the proposed confidential pricing agreement with the CMU, which is more representative of the true price of G/P if it were used in clinical practice than the base-case list price. This scenario therefore involved applying [redacted] The CMU price for OBV/PTV/RTV ± DSV was also applied in this scenario analysis.

2. A scenario analysis in which health state utility values for chronic HCV mild (F0–F1) and moderate (F2–F3) fibrosis and CC states are based on the baseline EQ-5D observations from all Phase III G/P clinical trials

[redacted]

In the trial-based health state utilities scenario analysis, the results were found to be in line with those of the base case analysis.

A.16 Innovation

G/P is a next-generation, oral, once-daily IFN- and RBV-free DAA regimen with antiviral activity against HCV genotypes 1–6, a high barrier to resistance, and a treatment duration as low as 8 weeks for TN NC patients, who represent the majority of HCV-infected individuals.[11] As such,

G/P is an innovative treatment that has a number of potential benefits compared to existing therapies, as follows:

1) G/P is an 8-week DAA regimen for TN NC patients across GT1–6. A duration of 8 weeks is also intended for TE NC patients with GT1, GT2, GT4, GT5 and GT6.

2) G/P was awarded PIM status and became available to address unmet needs for specific patients in the UK under the EAMS.[21] Such patient groups include:

   - **Patients with GT2, 3, 5 or 6 infection with CKD (Stage 4/5)**
   - **Patients with GT3 previously treated with peg-IFN, RBV and/or SOF**

3) The introduction of G/P may transform how CHC treatment is delivered to patients. Treatment with G/P could be delivered in primary care without the need for baseline RAV or viral load testing in patient groups within the anticipated licence, and also potentially without the requirement for genotyping. This would result in a simpler treatment-decision making process, helping to address a barrier to treatment in chaotic populations with high prevalence of CHC who could benefit from receiving treatment in the community.

A.17 End-of-life criteria

Not applicable

A.18 Budget impact

Table 13. Budget impact – Company budget impact analysis submission (page 19)

	Company estimate	Cross reference
Number of people in England who would have treatment	11997	Company budget impact analysis submission, Table 4
Average treatment cost	The anticipated list price per pack is £12,993.66. List price for treatment would therefore be £25,987.32 for 8 weeks of treatment, £38,980.98 for 12 weeks of treatment, and £51,974.64 for 16 weeks of treatment. The company is negotiating a pricing agreement with the Commercial Medicines Unit (CMU) such that [redacted]	Company budget impact

per person	[redacted]. This is pending acceptance at the time of submission. This is not a PAS but represents a negotiated confidential pricing agreement.	analysis submission, Table 5
Estimated annual budget impact on the NHS in England	List price for all treatments: –£48,061,535 *per annum* CMU price for G/P: [redacted] *per annum* The estimated budget impact at either list price or CMU price for G/P is negative, representing cost savings to the NHS in England.	Company budget impact analysis submission, Table 13 and Table 14

A.19 Interpretation and conclusions of the evidence

G/P is a pan-genotypic, highly effective and well-tolerated oral treatment regimen that has the potential to transform how CHC treatment is delivered to patients. Unlike existing DAA options, G/P is able to offer treatment durations as short as 8 weeks for GT1–6 infection in TN NC patients across all major genotypes. As a pan-genotypic treatment, a positive recommendation for G/P in TN NC patients across all 6 major genotypes regardless of IFN-eligibility would remove the need for baseline RAV and viral load testing in patient groups within the anticipated licence, and potentially remove the requirement for genotyping as well, because all TN NC patients within the anticipated licence for G/P would be eligible for an 8-week treatment course of G/P. Coupled with the simple, oral, once-daily administration of G/P it is thought that approval of G/P has the potential to move treatment provision to primary care and therefore help to address a barrier to treatment in groups of patients with high prevalence of HCV who would benefit from receiving treatment in the community, such as part of an outreach service. Such patient groups include intravenous drug users and patients on opiate substitution therapy who have difficulty engaging with secondary care services.

The base-case economic analysis applied list prices for all comparators and G/P. Of 26 subgroups (TN NC, TN CC, TE NC and TE CC for each of 6 genotypes, with GT2 TN NC and CC divided into IFN-eligible and IFN-ineligible), at a cost-effectiveness threshold of £20,000 per QALY gained, G/P was the cost-effective treatment in 13 of the 26 subgroups. In 12 of these subgroups G/P was associated with the lowest total costs, with G/P being dominant in 4 of these. In a pricing scenario analysis in which the price of G/P was aligned with the proposed confidential pricing agreement with the CMU and the CMU price for OBV/PTV/RTV ± DSV was applied [redacted]

[redacted]

References

1. Ansaldi F, Orsi A, Sticchi L, et al. Hepatitis C virus in the new era: perspectives in epidemiology, prevention, diagnostics and predictors of response to therapy. World J Gastroenterol 2014;20:9633-52.
2. Public Health England. Hepatitis C in the UK 2015 report. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/448710/NEW_FINAL_HCV_2015_IN_THE_UK_REPORT_28072015_v2.pdf [Last accessed February 2017]. 2015.
3. Patruni B, Nolte E. Hepatitis C: A Projection of the Healthcare and Economic Burden in the UK. Rand Health Q 2013;3:6.
4. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3:47-52.
5. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014;61:S58-68.
6. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2011;55:245-64.
7. NICE. NICE Guideline: Hepatitis C In development [GID-CGWAVE0666]. Volume 2017, 2016.
8. Eastern Liver Network. Management of Hepatitis C: Hepatitis C Guidelines v 8.1 09 June 2017.
9. Feld JJ, Moreno C, Trinh R, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks. J Hepatol 2016;64:301-7.
10. Asselah T, Hezode C, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin in adults with hepatitis C virus genotype 4 infection and cirrhosis (AGATE-I): a multicentre, phase 3, randomised open-label trial. Lancet Gastroenterol Hepatol 2016;1:25-35.
11. Adelphi Research UK. Patient tracker, Project reference 22968, 2017.
12. Public Health England. Improving access to, and completion of, hepatitis C treatment, 2015.
13. Public Health England. Hepatitis C in the UK. 2015 Report.
14. Public Health England. Hepatitis C in the UK. 2017 Report.
15. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015;61:77-87.
16. Hartwell D, Jones J, Baxter L, et al. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. Health Technol Assess 2011;15:i-xii, 1-210.
17. Ahmed A, Felmlee DJ. Mechanisms of Hepatitis C Viral Resistance to Direct Acting Antivirals. Viruses 2015;7:6716-29.
18. Chevaliez S, Pawlotsky JM. HCV Genome and Life Cycle. In: Tan SL, ed. Hepatitis C Viruses: Genomes and Molecular Biology. Norfolk (UK): Horizon Bioscience, 2006.
19. Poordad F, Felizarta F, Asatryan A, et al. Glecaprevir and Pibrentasvir for 12 Weeks for HCV Genotype 1 Infection and Prior Direct-acting Antiviral Treatment. Hepatology 2017;Epub ahead of print.
20. Ng TI, Krishnan P, Pilot-Matias T, et al. In Vitro Antiviral Activity and Resistance Profile of the Next Generation Hepatitis C Virus NS5A Inhibitor Pibrentasvir. Antimicrob Agents Chemother 2017.
21. MHRA. Early Access to Medicines Scientific Opinion - Public Assessment Report: Glecaprevir/Pibrentasvir 100mg/40mg film-coated tablets, 2016.
22. NICE. Sofosbuvir–velpatasvir for treating chronic hepatitis C: Technology appraisal guidance [TA430], 2017.
23. Zeuzem S, Feld J, Wang S, et al. ENDURANCE-1: A phase 3 evaluation of the efficacy and safety of 8- vs 12-week treatment with glecaprevir/pibrentasvir (formerly ABT-493/ABT-530) in HCV genotype 1-infected patients with or without HIV-1 co-infecition and without cirrhosis. AASLD. Boston, MA, 2016.
24. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Subjects With Genotype 1 Infection Study Record Detail. Available at: https://clinicaltrials.gov/ct2/show/record/NCT02604017?term=endurance-1&rank=2. Last accessed 9 May 2017.
25. AbbVie. Data on File: A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1 Infection

(ENDURANCE-1): Clinical Study Report R&D/16/0144 ABT-493/ABT-530 Protocol M13-590 (Primary Analysis), 2016.
26. Kowdley K, Colombi M, Zadeikis N, et al. ENDURANCE-2: Safety and efficacy of glecaprevir/pibrentasvir in hepatitis C virus genotype 2-infected patients without cirrhosis: a randomized, double-blind, placebo-controlled study. AASLD. Boston, MA, 2016.
27. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Subjects With Chronic Hepatitis C Virus (HCV) Genotype 2 Infection Study Record Detail. Available at: https://clinicaltrials.gov/ct2/show/NCT02640482?term=ENDURANCE-2&rank=1. Last accessed 9 May 2017.
28. AbbVie. Data on File: A Randomized, Double-Blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 2 Infection (ENDURANCE-2): Clinical Study Report R&D/16/0145 ABT-493/ABT-530 Protocol M15-464, 2016.
29. Foster G, Gane E, Asatryan A, et al. ENDURANCE-3: A phase 3, randomized, open-label, active-controlled study to compare efficacy and safety of ABT-493/ABT-530 to sofosbuvir co-administered with daclatasvir in adults with HCV genotype 3 infection. EASL. Barcelona, Spain, 2016.
30. ClinicalTrials.gov. A Study Comparing Efficacy and Safety of ABT-493/ABT-530 to Sofosbuvir Dosed With Daclatasvir in Adults With HCV Genotype 3 Infection (ENDURANCE-3). Available at: https://clinicaltrials.gov/ct2/show/NCT02640157?term=ENDURANCE-3&rank=1. Last accessed 9 May 2017.
31. AbbVie. Data on File: A Randomized, Open-Label, Active-Controlled, Multicenter Study to Compare Efficacy and Safety of ABT-493/ABT-530 to Sofosbuvir Co-Administered with Daclatasvir in Adults with Chronic Hepatitis C Virus Genotype 3 Infection (ENDURANCE-3): Clinical Study Report R&D/16/0162 ABT-493/ABT-530 Protocol M13-594 (Primary Analysis), 2016.
32. Asselah T, Hezode C, Zadeikis N, et al. ENDURANCE-4: Efficacy and safety of glecaprevir/pibrentasvir (formerly ABT-493/ABT-530) treatment in patients with chronic HCV genotype 4, 5 or 6 infection. AASLD. Boston, MA, 2016.
33. ClinicalTrials.gov. The Efficacy and Safety of ABT-493/ABT-530 in Adults With Chronic Hepatitis C Virus Genotype 4, 5, or 6 Infection (ENDURANCE-4). Available at: https://clinicaltrials.gov/ct2/show/NCT02636595?term=ENDURANCE-4&rank=1. Last accessed 9 May 2017.
34. AbbVie. Data on File: A Single-Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 4, 5, or 6 Infection (ENDURANCE-4): Clinical Study Report R&D/16/0157 ABT-493/ABT-530 Protocol M13-583 (Primary Analysis), 2016.
35. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults With Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis (EXPEDITION-1). Available at: https://clinicaltrials.gov/ct2/show/NCT02642432?term=EXPEDITION-1&rank=1. Last accessed 9 May 2017.
36. AbbVie. Data on File: A Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis (EXPEDITION-1): Clinical Study Report R&D/16/0158 ABT-493/ABT-530 Protocol M14-172 (Primary Analysis), 2016.
37. Muir A, Strasser S, Wang S, et al. High SVR rates with ABT-493 + ABT-530 co-administered for 8 weeks in non-cirrhotic patients with HCV genotype 3 infection. EASL. Barcelona, Spain, 2016.
38. Kwo P, Poordad F, Porcalla A, et al. Safety of ABT-493 + ABT-530 co-administered in patients with HCV genotype 1-6 infection: results from SURVEYOR-I and SURVEYOR-II studies. EASL. Barcelona, Spain, 2016.
39. Poordad F, Kwo P, Hassanein T, et al. High SVR rates with ABT-493 + ABT-530 in non-cirrhotic patients with HCV genotypes 1, 2, 3 infection. APASL. Tokyo, Japan, 2016.
40. Kwo P, Bennet M, Wang S, et al. SURVEYOR-II: High SVR4 rates achieved with the next generation NS3/4A protease inhibitor ABT-493 and NS5A inhibitor ABT-530 in non-cirrhotic treatment-naive and treatment-experienced patients with HCV genotype 3 infection. AASLD. San Francisco, CA, 2015.

41. Poordad F, Felizarta F, Wang S, et al. High SVR rates with a combination of ABT-493 + ABT-530 for 8 weeks in non-cirrhotic patients with HCV genotype 1 or 2 infection. EASL. Barcelona, Spain, 2016.
42. ClinicalTrials.gov. A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without RBV in Subjects With Chronic Hepatitis C Virus (HCV) Genotypes 2, 3, 4, 5 or 6 Infection. Available at: https://clinicaltrials.gov/ct2/show/NCT02243293?term=surveyor-ii&rank=1. Last accessed 9 May 2017.
43. AbbVie. Data on File: A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without RBV in Subjects With Chronic Hepatitis C Virus (HCV) Genotypes 2, 3, 4, 5 or 6 Infection (SURVEYOR-II): Clinical Study Report R&D/15/1230 ABT-493, ABT-530, ABT-493/ABT-530 Protocol M14-868 (Primary Analysis), 2016.
44. Wyles D, Poordad F, Wang S, et al. SURVEYOR-II, Part 3: Efficacy and Safety of glecaprevir/pibrentasvir (ABT-493/ABT-530) in patients with hepatitis C virus genotype 3 infection with prior treatment experience and/or cirrhosis. AASLD. Boston, MA, 2016.
45. AbbVie. Data on File: An Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without Ribavirin in Subjects with Chronic Hepatitis C Virus (HCV) Genotype 1, 4, 5, and 6 Infection (SURVEYOR-I): Clinical Study Report R&D/15/1229 ABT-493, ABT-530 Protocol M14-867, 2016.
46. ClinicalTrials.gov. A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-administration of ABT-493 and ABT-530 With and Without Ribavirin in Subjects With HCV Genotype 1, 4, 5, and 6 Infection. Available at: https://clinicaltrials.gov/ct2/show/NCT02243280?term=surveyor-i&rank=1. Last accessed 9 May 2017.
47. Gane E, Lalezari J, Asatryan A, et al. 100% SVR4 and favorable safety of ABT-493 + ABT-530 administered for 12 weeks in non-cirrhotic patients with genotypes 4, 5, or 6 infection (SURVEYOR-I). EASL. Barcelona, Spain, 2016.
48. Wyles D, Sulkowski M, Wang S, et al. SURVEYOR-II: High SVR4 rates achieved with next generation NS3/4A protease inhibitor ABT-493 and NS5A inhibitor ABT-530 in non-cirrhotic treatment-naive and treatment-experienced patients with HCV genotype 2 infection. AASLD. San Francisco, CA, 2015.
49. Hassanein T, Wyles D, Wang S, et al. SURVEYOR-II, Part 4: Glecaprevir/pibrentasvir demonstrates high SVR rates in patients with HCV genotype 2, 4, 5, or 6 infection without cirrhosis following an 8-week treatment duration. AASLD. Bostom, MA, 2016.
50. Gane D, Lawitz E, Pugatch D, et al. EXPEDITION-4: Efficacy and safety of glecaprevir/pibrentasvir (ABT-493/ABT-530) in patients with renal impairment and chronic hepatitis C virus genotype 1-6 infection. AASLD. Boston, MA, 2016.
51. AbbVie. Data on File: A Single-Arm, Open-Label, Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Renally-Impaired Adults with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (EXPEDITION-4): Clinical Study Report R&D/16/0159 ABT-493/ABT-530 Protocol M15-462 (Primary Analysis), 2016.
52. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Renally Impaired Adults With Chronic Hepatitis C Virus Genotype 1 - 6 Infection (EXPEDITION-4). Available at: https://clinicaltrials.gov/ct2/show/NCT02651194?term=expedition-4&rank=1. Last accessed 9 May 2017.
53. AbbVie. Data on File: A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 (or ABT-493/ABT-530) With and Without Ribavirin in Adults With Chronic Hepatitis C Virus (HCV) Infection Who Failed a Prior Direct-Acting Antiviral Agent (DAA)-Containing Therapy: Clinical Study Report R&D/16/0160 ABT-493, ABT-530, ABT-493/ABT-530 Protocol M15-410 (Primary Analysis), 2016.
54. Poordad F, Gordon S, Asatryan A, et al. High efficacy of ABT-493 and ABT-530 in HCV genotype-1 infected patients who have failed direct-acting antiviral-containing regimens: the MAGELLAN-I study. EASL. Barcelona, Spain, 2016.
55. Poordad F, Felizarta F, Asatryan A, et al. Glecaprevir and Pibrentasvir for 12 Weeks for HCV Genotype 1 Infection and Prior Direct-acting Antiviral Treatment. Hepatology 2017;Epub ahead of print.

56. ClinicalTrials.gov. A Study to Evaluate the Safety and Efficacy of ABT-493/ABT-530 in Adult Post-Liver or Post-Renal Transplant Recipients With Chronic Hepatitis C Virus (MAGELLAN-2). Available at: https://clinicaltrials.gov/ct2/show/NCT02692703?term=magellan-2&rank=1. Last accessed 9 May 2017.
57. Poordad F, Pol S, Asatryan A, et al. MAGELLAN-1, Part 2: Glecaprevir and pibrentasvir for 12 or 16 weeks in patients with chronic hepatitis C virus genotype 1 or 4 and prior direct-acting antiviral treatment failure. EASL. Amsterdam, the Netherlands, 2017.
58. Pilot-Matias T, Krisnan P, Schnell G, et al. Resistance analysis in the MAGELLAN-I study (Part 2): Glecaprevir/pibrentasvir therapy in HCV-infected patients who had failed prior DAA regimens containing NS3/4A protease and/or NS5A inhibitors. EASL. Amsterdam, the Netherlands, 2017.
59. AbbVie. Data on File: Glecaprevir/Pibrentasvir Summary of Clinical Efficacy, 2016.
60. Foster G, Gane E, Asatryan A, et al. ENDURANCE-3: safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naïve HCV genotype 3-infected patients without cirrhosis. EASL. Amsterdam, the Netherlands, 2017.
61. Liu S, Cipriano LE, Holodniy M, et al. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Ann Intern Med 2012;156:279-90.
62. Johnson SJ, Parise H, Virabhak S, et al. Economic evaluation of ombitasvir/paritaprevir/ritonavir and dasabuvir for the treatment of chronic genotype 1 hepatitis c virus infection. J Med Econ 2016;19:983-94.
63. Salomon JA, Weinstein MC, Hammitt JK, et al. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. JAMA 2003;290:228-37.
64. Shepherd J, Jones J, Hartwell D, et al. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess 2007;11:1-205, iii.
65. Grieve R, Roberts J, Wright M, et al. Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. Gut 2006;55:1332-8.
66. NICE. Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C: Technology appraisal guidance [TA365], 2015.
67. Thein HH, Yi Q, Dore GJ, et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48:418-31.
68. NICE. Daclatasvir for treating chronic hepatitis C: Technology appraisal guidance [TA364], 2015.
69. Kanwal F, Kramer JR, Ilyas J, et al. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. Hepatology 2014;60:98-105.
70. Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol 2010;52:652-7.
71. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463-72.
72. Bennett WG, Inoue Y, Beck JR, et al. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. Ann Intern Med 1997;127:855-65.
73. NICE. Final appraisal determination: Sofosbuvir–velpatasvir for treating chronic hepatitis C, 2016.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Glecaprevir/pibrentasvir for treating chronic hepatitis C [ID1085]

Document B

Company evidence submission

AbbVie Ltd

July 2017

File name	Version	Contains confidential information	Date
2a. ID 1085 [Redacted]_GP (Maviret)_NICE Document B_FINAL_Amended CI 18.10.17	1	No	18/10/2017

Instructions for companies

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

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

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

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

Highlighting in the template (excluding the contents list)

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

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables

Figures

Abbreviations

3TC	Lamivudine
Ab	Antibody
ABC	Abacavir
ADR	Adverse drug reactions
AE	Adverse event
AFP	Alpha-fetoprotein
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APRI	Aminotransferase/platelet ratio index
ART	Anti-retroviral treatment
ASV	Asunaprevir
AZT	Zidovudine
BCR	Benefit cost ratio
BD	Twice-daily
BIM	Budget impact model
BNF	British National Formulary
BOC	Boceprevir
BP	Baseline polymorphism
BSC	Best supportive care
C	Cirrhotic
CC	Compensated cirrhosis
CFB	Change from baseline
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
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAA	Direct-acting antiviral
DAE	Discontinuations relating to adverse events
DB	Double-blind
DCC	Decompensated cirrhosis
DCV	Daclatasvir
DoH	Department of Health
DSA	Deterministic sensitivity analysis
DSV	Dasabuvir
DTG	Dolutegravir

EAMS	Early Access to Medicines Scheme
EAP	Early Access Programme
EASL	European Association for the Study of the Liver
EBR	Elbasvir
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EODBT	End of double-blinded treatment
EOT	End of treatment
EQ-5D-3L	EuroQol-5 Dimensions-three Level
EQ-5D-5L	EuroQol-5 Dimensions-five Level
ERG	Evidence Review Group
ESLD	End-stage liver disease
FAD	Final appraisal determination
FBC	Full blood count
FDC	Fixed dose comparison
FIB	Fibrosis
FSS	Fatigue Severity Scale
FTC	Emtricitabine
GGT	Gamma-glutamyl transferase
GLE	Glecaprevir
GP	General practitioner
GT	Genotype
GZR	Grazoprevir
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCHS	Hospital and Community Health Service
HCV	Hepatitis C virus
HCVTSat	Chronic HCV treatment satisfaction instrument
HIV	Human immunodeficiency virus
HOMA-IR	Homeostatic model assessment of insulin resistance
HRQoL	Health-related quality of life
HTA	Health technology assessment
HTLV	Human T-lymphotropic virus
HUI3	Health Utilities Index Mark 3
ICD	International Classification of Disease
ICER	Incremental cost-effectiveness ratio
IDU	Injecting drug use
IFN	Interferon
IgG	Immunoglobulin G
INMB	Incremental net monetary benefit
INR	International normalised ratio

IQR	Interquartile range
IRT	Interactive response technology
ITC	Indirect treatment comparison
ITT	Intention-to-treat
ITT-MS	ITT mono-infected HCV GT1 population
ITT-PS	ITT mono-infected GT1 DAA-naïve
ITT-PS-PP	Per-protocol ITT-PS population
KOL	Key opinion leader
LCB	Lower confidence-bond
LDV	Ledipasvir
LFT	Liver function test
LLN	Lower limit of quantitation
LLOQ	Lower limit of quantitation
LSMD	Least squares mean difference
LT	Liver transplant
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MCS	Mental component summary
MDRD	Modification of Diet in Renal Disease
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
MRU	Medical resources utilisation
MTC	Mixed treatment comparison
N/A	Not applicable
N	No
NC	Non-cirrhotic
NGS	Next generation sequencing
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NHSE	National Health Service England
NHWS	National Health and Wellness Survey
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NS	Non-structural
OAE	Overall adverse events
OBV	Ombitasvir
OD	Once-daily
OL	Open label
ONS	Office of National Statistics
P-gp	P-glycoprotein
PAS	Patient Access Scheme

PCR	Polymerase chain reaction
peg-IFN	Pegylated IFN
PIB	Pibrentasvir
PII	Phase II
PIII	Phase III
PIM	Promising Innovative Medicine
PKT	Post-kidney transplant
PLT	Post-liver transplant
PP	Per person
PPI	Proton pump inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRO	Patient reported outcome
PSA	Probabalistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PTV	Paritaprevir
PWID	People who inject drugs
QALY	Quality-adjusted life year
RAV	Resistance associated variant
RBV	Ribavirin
RCT	Randomised controlled trial
RE	Role-limitations emotional
RGT	Response-guided therapy
RNA	Ribonucleic acid
RPV	Rilpivirine
RTV	Ritonavir
SAE	Serious adverse event
SC	Subcutaneously
SD	Standard deviation
SE	Standard error
SF	Social functioning
SF-36v2	SF-36 version 2
SF-6D	Short-Form Six-Dimension
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMV	Simeprevir
SoC	Standard of care
SOF	Sofosbuvir
STA	Single technology appraisal
SVR	Sustained virologic response
TA	Technology appraisal
TDF	Tenofovir disoproxil fumarate
TE	Treatment-experienced

TE-PR	TE with regimens containing peg-IFN/RBV
TE-PRS	TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN
TFT	Thyroid function test
TN	Treatment-naïve
TVR	Telaprevir
UGT	Uridine glucuronyl transferase
ULN	Upper limit of normal
US	United States of America
UTD	Unable to determine
VAS	Visual analogue scale
VEL	Velpatasvir
VOX	Voxilaprevir
WHO	World Health Organisation
WPAI-HCV	Work Productivity Activity Impairment Hepatitis C Specific Instrument
WTP	Willingness-to-pay threshold

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

B.1.1 *Decision problem*

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with CHC: • who have not had treatment for CHC before (TN) • who have had treatment for CHC before (TE)	Per final scope	N/A
Intervention	Glecaprevir/pibrentasvir; referred to in this submission as G/P	Per final scope	N/A
Comparator(s)	• Best supportive care (no active pharmacological treatment) (GT1-6) • DCV in combination with SOF, with or without RBV (for specific people with GT1, GT3 or GT4; as recommended by NICE) • EBR/GZR (for GT1 or GT4) • SOF/LDV (for specific people with GT1 or GT4; as recommended by NICE) • OBV/PTV/RTV with or without DSV or RBV (for GT1 or GT4)	• Best supportive care (no active pharmacological treatment) (GT1–6) • DCV in combination with SOF without RBV (for GT3 only, as recommended by NICE) • EBR/GZR (for GT1 or GT4) • SOF/LDV (for specific people with GT1 or GT4; as recommended by NICE) • OBV/PTV/RTV with or without DSV or RBV (for GT1 or GT4)	The following comparators were excluded as they are not used in current NHS practice: • DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE) • PegIFNα with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients) • SOF in combination with RBV, with or without pegIFNα (for specific people

	• PegIFNα with RBV (for GT1– 6) • SOF in combination with RBV, with or without pegIFNα (for specific people with GT1–6; as recommended by NICE) • SOF/VEL (for specific people with GT1–6; as recommended by NICE)	• PegIFNα with RBV for GT2 non-cirrhotic treatment-naïve patients only • SOF in combination with RBV, with or without pegIFNα (for specific people with GT2, GT3, GT5 and GT6, as recommended by NICE) • SOF/VEL (for specific people with GT1–6; as recommended by NICE)	with GT1 and GT4; as recommended by NICE)
Outcomes	The outcome measures to be considered include: • mortality • SVR • development of resistance to treatment • adverse effects of treatment • HRQoL	Per final scope	N/A
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • genotype • co-infection with HIV • people with and without cirrhosis • previous treatment received (with or without DAA-containing regimens) • people who have received treatment before liver transplantation, and	Clinical evidence for these subgroups is presented where this is available. The economic analyses are stratified by genotype, cirrhosis status and previous treatment history (naïve or experienced), in line with recent prior NICE appraisals. Separate comparators for IFN-eligible and IFN-ineligible subgroups were also considered in line with NICE guidance.	Patients co-infected with HCV/HIV-1 are modelled as the same as those with HCV mono-infection. This is consistent with the approach taken in TA430.[1] The analyses split patients into TN and TE, where the TE group was defined as patients who have not adequately responded to prior IFN/RBV-based treatment with or without SOF, in line with the clinical trial programme for G/P and its anticipated licence.

	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 • people with and without renal impairment		Separate economic subgroup analyses are not performed for TE patients stratified by previous treatment response. This is in line with the fact that neither NICE TA guidance nor the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1) provides distinct treatment recommendations on the basis of different previous treatment response.[2] Subgroup analyses were not performed in patients who had previously received treatment with NS3/4A- or NS5A inhibitors as G/P is currently not anticipated to be licensed in these patients. Separate economic subgroup analyses were also not performed for patients who have received a liver transplant or for patients with renal impairment. The submission already considers an extensive number of subgroups subdivided by genotype, treatment history and cirrhosis status. Further subgroup analyses were therefore not performed, in order to focus the decision problem on the subgroups defined by genotype, treatment experience and cirrhosis status around which NICE treatment recommendations are based.
Special considerations including issues related to equity or equality	If the evidence allows, the impact of treatment on reduced onward HCV transmission will also be considered.	Onward transmission is not included in the economic model.	Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework.

Abbreviations: CHC, chronic hepatitis C; DAA, directly-acting antiviral; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GZR, grazoprevir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IFN, interferon; LDV, ledipasvir; N/A, not applicable; OBV, ombitasvir; PTV, paritaprevir; peg-IFN, pegylated IFN; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TA, technology appraisal; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

B.1.2 *Description of the technology being appraised*

Table 2: Technology being appraised

UK approved name and brand name	Glecaprevir/pibrentasvir (Maviret®); referred to in this submission as G/P
Mechanism of action	G/P comprises a combination of two DAAs that have individual mechanisms of action against HCV: glecaprevir (ABT-493) inhibits the NS3/4A protease whilst pibrentasvir (ABT-530) inhibits the NS5A protein. As a result, G/P interferes with multiple, key steps in the viral lifecycle. The NS3/4A protease is a heterodimer complex of NS3 and NS4A proteins, whereby NS3 contains a serine protease domain and the central region of NS4A functions as a cofactor for protease activity.[3, 4] The protease is responsible for catalysing the breakdown of the HCV encoded polyprotein into NS3, NS4A, NS4B, NS5A and NS5B non-structural (NS) proteins, which are required for viral replication.[3] Glecaprevir blocks the activity of the NS3/4A protease, and so impairs HCV replication.[5] The NS5A protein plays a crucial role in HCV replication, and is also involved in the assembly and release of virions into the surrounding extracellular fluid.[3] The protein has three domains: domains I and II take part in RNA replication, whereas domain III is integral for the assembly of HCV particles.[3] Pibrentasvir, as an NS5A inhibitor, causes conformational changes in the NS5A protein upon binding, which prevents it from interacting with other proteins in the viral membrane and host cell. As a result, HCV is left unable to form the replicase complex, and so cannot replicate its RNA.[3, 6]
Marketing authorisation/CE mark status	G/P (Maviret®) was reviewed under the EMA's accelerated assessment program, with a CHMP positive opinion adoption at Day-120 of the procedure. Full marketing authorisation is currently anticipated by late July or early August. G/P is currently available to patients meeting certain clinical criteria in the UK via an Early Access to Medicines Scheme.[7]
Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC)	On June 22, 2017, the CHMP adopted a positive opinion, recommending the granting of marketing authorisation for Maviret®. The therapeutic indication for Maviret® is the treatment of chronic hepatitis C virus (HCV) infection in adults.
Method of administration and dosage	Oral administration of 100 mg / 40 mg film-coated tablets. Three tablets taken together once daily (300 mg / 120 mg OD), with food, for 8 weeks, 12 weeks or 16 weeks as shown in Table 3. **Table 3: Treatment duration for anticipated licence** **Patient population** / **NC** / **CC** **TN** / 8 weeks for all genotypes / 12 weeks for all genotypes

	TE, previously treated with: • Peg-IFN + RBV • SOF + peg-IFN + RBV • SOF + RBV	GT1,2, 4–6: 8 weeks GT3: 16 weeks	GT1, 2, 4–6: 12 weeks GT3: 16 weeks
	Abbreviations: CC, compensated cirrhosis; GT, genotype; NC, non-cirrhotic; peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve		
Additional tests or investigations	No additional tests or investigations beyond those that are already standard practice for diagnosis of CHC are required.		
List price and average cost of a course of treatment	The list price per pack is £12,993.66. List price for treatment would therefore be £25,987.32 for 8 weeks of treatment, £38,980.98 for 12 weeks of treatment, and £51,974.64 for 16 weeks of treatment.		
Patient access scheme (if applicable)	The company is negotiating a pricing agreement with the CMU such that the total regimen cost of G/P is [redacted]. This is pending acceptance at the time of submission. This is not a PAS but represents a negotiated confidential pricing agreement.		

Abbreviations: CHC, chronic hepatitis C; CHMP, Committee for Medicinal Products for Human Use; CMU, Commercial Medicines Unit; DAA, directly-acting antiviral; EMA, European Medicines Agency; G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; NS, non-structural; OD, once daily; RNA, ribonucleic acid; PAS, Patient Access Scheme; SmPC, Summary of Product Characteristics; SVR, sustained virologic response

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

B.1.3.1 Disease overview

Hepatitis C virus (HCV) infection represents a severe burden on patients and healthcare systems around the world. The global prevalence of infection with HCV has risen from 2.3% to 2.8% over the last 15 years, corresponding to a chronically infected population worldwide of approximately 170 million people, with 3–4 million new cases of HCV infection globally every year.[3]

Six major genotypes (GT1–6) and 67 subtypes of HCV have currently been identified, with high sequence diversity existing between the genotypes (30%) and subtypes (20%).[8] Within the United Kingdom (UK), GT1 and GT3 are most prevalent. In England, these genotypes account for 47% and 44% of HCV infection cases, respectively, with the other genotypes contributing the remaining 9%.[9] Importantly, GT3 is associated with the highest risk of developing cirrhosis and hepatocellular carcinoma (HCC).[9]

Acute HCV infection is mostly asymptomatic; approximately 20–30% of patients present with clinical symptoms. Symptoms are normally mild and non-specific, such as malaise, and typically

present 3 to 12 weeks post viral exposure.[10] Indeed, in the UK, it has been suggested that 86% of individuals infected with the virus are unaware they have been infected; this presents a clear issue for heightened risk of onward transmission.[11] Therefore, whilst approximately 15–25% of patients with acute HCV infection clear the viral ribonucleic acid (RNA) spontaneously within 6 months, the remaining 75–85% of patients progress to chronic hepatitis C (CHC) infection, as defined by the presence of serum HCV RNA for >6 months.[10]

Chronic HCV infection induces injury and inflammation of the liver, resulting in fibrosis (an excessive accumulation of scar tissue). Depending on whether co-factors are present (e.g. alcohol consumption), 10–20% of patients progress to cirrhosis over 20–30 years, and because of the asymptomatic nature of the condition initially, it is not uncommon for patients to remain unaware they are infected with HCV until they present with complications associated with cirrhosis.[12, 13] In the initial compensated form of cirrhosis (compensated cirrhosis; CC), the liver is able to "compensate" for the damage caused to areas by the extensive fibrosis.[10] However, once cirrhosis has developed patients have a 1–5% annual risk of progression to decompensated cirrhosis (DCC), a term that signifies that the liver is no longer able to carry out its normal functioning (i.e. can no longer compensate for the damage suffered).[12] DCC is associated with the development of a variety of complications including variceal haemorrhage, ascites and hepatic encephalopathy.[10] The severity of DCC can be evidenced by a fall in the 5-year survival rate from 91% when compensated to 50% when the liver decompensates; patients who have an episode of decompensation have a 15–20% risk of death in the subsequent year.[10,12]

CHC is also associated with several extra-hepatic manifestations, including the development of mixed cryoglobulinaemia and its sequelae (ranging from cutaneous and visceral vasculitis to glomerulonephritis and B-cell non-Hodgkin's lymphoma), as well as increased rates of insulin resistance, diabetes, and atherosclerosis, which may lead to increased cardiovascular morbidity and mortality.[14] Neurological manifestations of HCV infection include fatigue and cognitive impairment.[14]

Patients with cirrhosis due to CHC are ultimately at risk of progressing to end-stage liver disease (ESLD) or developing HCC, both of which represent serious liver conditions. The annual risk of patients developing HCC for patients with cirrhosis is 1–5%.[12] In the United States (US), Australia and Europe, the principal form of long-term treatment for patients with DCC and HCC is liver transplantation.[10]

B.1.3.2 Impact on patients, carers and society

It has been established that health-related quality of life (HRQoL) is lower in individuals suffering from CHC compared to the general population, with increasing severity of liver disease associated with further worsening of HRQoL.[15] Current treatment options may also pose a considerable burden on HRQoL for some patient subgroups. For example, according to NICE guidance (TA430), the only treatment option for interferon (IFN)-eligible, treatment-naïve (TN) GT2 patients without cirrhosis is dual-therapy with pegylated interferon alpha (peg-IFNα) and ribavirin (RBV).[16] Treatment with peg-IFNα plus RBV is associated with a variety of toxic side-effects.[17]

CHC places a significant burden on healthcare resources worldwide, with CHC-related costs found to increase with disease severity, with progression of patients to ESLD requiring transplantation, posing a considerable cost to the National Health Service (NHS).[15, 18] Indirect costs of HCV to society are also significant. A recent survey of 57,805 participants across 5

European countries (including the UK) demonstrated that HCV-infected patients were more impaired at work compared to healthy, matched controls (30% vs. 18%, p <0.001), as well as in non-work related activities (34% vs. 28%, p <0.05), as measured by the Work Productivity and Activity Impairment (WPAI) questionnaire.[19] Moreover, HCV patients had a significantly greater loss of earnings due to impaired productivity compared to their healthy counterparts (€6,414 vs. €3,642, p <0.05).[19]

B.1.3.3 Life expectancy

In addition to the morbidity associated with CHC, CHC is also associated significant mortality once patients progress to DCC, ESLD or HCC. Notably, liver disease is quoted as the only major cause of death in England where the annual rate is currently rising, with an average age of death at 59 years (26–30 years younger than the most common age at death in the UK).[20, 21] One study conducted in the UK has demonstrated mortality rates amongst HCV-infected patients to be three times higher than expected relative to the general population of England.[22] However, the introduction of new direct-acting antiviral (DAA) drugs may be starting to have an impact on HCV-related mortality, with a fall of 8% in HCV-related ESLD and HCC deaths in 2015.[23]

It has been shown that cirrhosis independently raises the annual rate of mortality among patients with CHC, with DCC having a higher mortality than CC (6.6% vs. 3.9%, p=0.01).[24] Furthermore, the post-transplant mortality rate in patients with HCV post-liver transplantation is 31.0%, with a post-transplant survival of 64.7% after 5 years. Notably, a multivariate analysis demonstrated that diagnosing HCV infection in individuals with HCC was independently associated with a greater risk of liver transplant failure and mortality (p <0.0001) compared to other causes of HCC.[25]

B.1.4 *Clinical pathway of care*

The aim of treatment is a sustained virologic response (SVR), meaning complete clearance of the virus and cure. For CHC patients for whom treatment does not provide successful cure and who progress to ESLD and/or HCC, the main form of treatment is liver transplantation.[10]

When considering treatment of CHC in England specifically, review of current NICE technology appraisal (TA) guidance provides a summary of the treatments available as potential therapeutic options for a given CHC patient subgroup. There is no NICE clinical guideline for hepatitis C to then distinguish which of the NICE-recommended therapies might represent standard of care. This is because in January 2014 the development of a hepatitis C clinical guideline by NICE was paused until NICE TAs evaluating new pharmacological therapies had been published.[26] As of September 2016, NICE has decided that the development of this guideline should remain paused until there is stability in the availability of treatments and the cost to the NHS of pharmacological therapies for this condition.[26]

Table 4 presents a matrix of NICE-recommended therapies organised by genotype, cirrhosis status and treatment history. Currently, the only DAA regimen without IFN and/or RBV that has a recommendation in all 6 genotype populations of HCV infection is sofosbuvir/velpatasvir (SOF/VEL, brand name Epclusa®). However, in GT2 SOF/VEL is only recommended for TN non-cirrhotic (NC) patients who cannot tolerate IFN-based treatments.

Table 4. Matrix of NICE-recommended therapies for CHC

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	C	NC	C
1	• SOF/VEL (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (24/48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • SOF/LDV (8) • OBV/PTV/RTV + DSV (12), 1a: + RBV • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (24), or peg-IFN + RBV (4) then BOC + peg-IFN + RBV (32) then peg-IFN + RBV (12)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (12), or TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) **Treatments only recommended for patients with significant fibrosis[c]:** • SOF + DCV (12)	• SOF/VEL[+] (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (24/48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • *SOF/LDV (12) • *OBV/PTV/RTV + DSV + RBV (12), 1a: (24)[b] • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • *SOF + DCV ± RBV (24)	• SOF/VEL (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • SOF/LDV (12) • OBV/PTV/RTV + DSV (12), 1a: + RBV • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (32) then peg-IFN + RBV (12), or peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (12), or TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) **Treatments only recommended for patients with significant fibrosis[c]:** • SOF + DCV (12)	• SOF/VEL[+] (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • *SOF/LDV[a] (12) • *OBV/PTV/RTV + DSV + RBV (12), 1a: (24)[b] • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • *SOF + DCV ± RBV (24)

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	C	NC	C
2	• Peg-IFN + RBV (24) • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • SOF/VEL (12) • SOF + RBV (12)	• SOF/VEL[+] (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • SOF + RBV (12)	• SOF/VEL[+] (12) • SOF + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL[+] (12) • SOF + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)
3	• SOF/VEL (12) • Peg-IFN + RBV (24) • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:** • SOF + DCV (12)	• SOF/VEL[+] ± RBV (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • SOF + RBV (24) • *SOF + DCV + RBV (24)	• SOF/VEL (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:** • SOF + DCV (12)	• SOF/VEL[+] ± RBV (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • SOF + RBV (24) • *SOF + DCV + RBV (24)

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	C	NC	C
4	• SOF/VEL (12) • *Peg-IFN + RBV (24/48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • OBV/PTV/RTV + RBV (12) • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12)* • Best supportive care (watchful waiting) **Treatments only recommended for patients with significant fibrosis[c]:** • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* **Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:** • *SOF + DCV (12)*	• SOF/VEL[+] (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (24/48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • *SOF/LDV (12) • OBV/PTV/RTV + RBV (24)[b] • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12)* • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • **SOF + DCV ± RBV (24)*	• SOF/VEL (12) • *Peg-IFN + RBV (48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • SOF/LDV (12) • OBV/PTV/RTV + RBV (12) • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12/36)* • Best supportive care (watchful waiting) **Treatments only recommended for patients with significant fibrosis[c]:** • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* **Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:** • *SOF + DCV (12)*	• SOF/VEL[+] (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • *SOF/LDV[a] (12) • OBV/PTV/RTV + RBV (24)[b] • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12/36)* • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* • Best supportive care (watchful waiting) **Treatments only recommended for IFN-ineligible patients:** • **SOF + DCV ± RBV (24)*

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	C	NC	C
5 or 6	• SOF/VEL (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL+ (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL+ (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)

*CC only (i.e. not recommended for DCC)
+ + RBV if DCC
[a]Recommended only if all the following criteria are met: Child-Pugh class A, platelet count of 75,000/mm^3 or more, no features of portal hypertension, no history of HCV-associated decompensation episode and not previously treated with an NS5A inhibitor; [b]TA365 for OBV/PTV/RTV ± DSV was published before the results from TURQUOISE-III and AGATE-I became available and the NICE recommendation therefore stipulates the use of OBV/PTV/RTV ± DSV with RBV for GT1b patients with CC, and OBV/PTV/RTV + RBV for GT4 CC patients for 24 weeks. Subsequently, TURQUOISE-III demonstrated the efficacy of treatment with OBV/PTV/RTV + DSV for 12 weeks without RBV in GT1b patients with CC,[27] and AGATE-I demonstrated the efficacy of OBV/PTV/RTV + RBV for 12 weeks in GT4 patients with CC.[28] The licence for OBV/PTV/RTV ± DSV now reflects this. Therefore OBV/PTV/RTV + DSV without RBV for 12 weeks is used as the comparator in the economic analysis of this submission for GT1b patients with CC, and OBV/PTV/RTV + RBV for 24 weeks is used for GT4 CC patients; [c]Significant fibrosis is defined as METAVIR fibrosis stage F3 and F4.
Abbreviations: BOC, boceprevir; C, cirrhotic; CC, compensated cirrhosis; DCC, decompensated cirrhosis; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; peg-IFN, pegylated-IFN; PTV, paritaprevir; RAV, resistance associated variant; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; TN, treatment-naïve; TE, treatment-experienced; VEL, velpatasvir
Therapies highlighted in *grey italics* represent therapies that, although associated with a positive NICE recommendation for use in the NHS, no longer form part of current clinical practice and are therefore not considered as comparators to G/P in this submission

Table 4 demonstrates the complex picture of available treatment choices as per current NICE guidance. However, it should be noted that whilst Table 4 presents a list of technologies that have existing NICE guidance and are therefore theoretically available on the NHS, a number of these therapies do not constitute a part of current clinical practice in England. These therapies are in *grey italics* in Table 4 and specific considerations for why each of these therapies no longer represents current clinical practice is described below. These considerations are based on expert clinical opinion as well as review of the treatment options specified in the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1),[2] which also include an NHS England (NHSE) determined 'rate card'. The 'rate card' is an NHSE term used to describe therapies which were awarded contracts with NHSE based on the tender outcomes.[2] The 'rate card' also assigns a sequence of use, i.e. it specifies 1st, 2nd and 3rd line treatment and there is a CQUIN (Commissioning for Quality and Innovation payments framework) which incentivises the alignment of specialist led multidisciplinary team (MDT) decisions with NHS England published rate cards. It is therefore reasonable to assume that only therapies listed on the rate card will be used within NHSE and form current clinical practice.

- **Boceprevir (BOC)** and **telaprevir (TVR) (both taken with peg-IFNα + RBV**) are not currently used in clinical practice because the toxicity associated with peg-IFNα plus RBV is worsened by the addition of BOC and TVR. This was noted and accepted by the NICE Committee in TA430; therefore neither BOC or TVR should be considered as comparators to G/P in this appraisal, as reflected by their omission from the final scope for this appraisal.
- **Daclatasvir (DCV) + peg-IFNα + RBV** is not used in the treatment of GT4 due to the availability of several IFN-free regimens for this population. This was noted and accepted by the NICE Committee in TA430; therefore it is acknowledged that DCV + peg-IFNα + RBV is not used in clinical practice and therefore is not considered as a comparator to G/P in this appraisal, as reflected by its omission from the final scope for this appraisal.
- **Simeprevir (SMV) + peg-IFNα + RBV** is similarly not used in the treatment of GT4, for the same reason as given above for DCV + peg-IFNα + RBV; again, this was accepted by the NICE Committee in TA430 and therefore SMV + peg-IFNα + RBV is not considered as a comparator to G/P in this appraisal, as reflected by its omission from the final scope for this appraisal.
- Use of **peg-IFNα + RBV alone** has been gradually reducing in clinical practice since the introduction of newer DAAs, which provide higher rates of response with a shorter treatment duration and have, for a number of patient populations, provided treatment options that avoid the requirement for patients to receive peg-IFNα ± RBV. IFN-based regimens are associated with adverse events (AEs) that typically include the onset of multiple constitutional symptoms, such as flu-like symptoms, nausea, headache and weight loss, and which can lead to irreversible complications.[1, 29] It is therefore highly desirable for patients with HCV to avoid treatment involving IFN-based regimens where possible; indeed in some cases patients refuse treatment with peg-IFNα and instead risk future HCV-related complications.[1] This is reflected in the latest (2016) treatment guidelines from the European Association for the Study of the Liver (EASL), which note that "in 2016 and onwards, IFN-free regimens are the best options in treatment-naïve and treatment-experienced, DAA-naïve patients with compensated and decompensated liver disease, because of their virological efficacy, ease of use and tolerability" and that the advent of new DAAs implies that the use of regimens involving peg-IFNα and RBV is no longer recommended.[13]

In the most recent technology appraisal for CHC (SOF/VEL, TA430), it was noted that whilst use of peg-IFNα + RBV is reducing, at the time of that appraisal it represented the first choice treatment for patients with mild, untreated GT2 infection, and its use in other genotypes had not completely stopped. However, SOF/VEL received a positive recommendation across GT1 and GT3–6 as part of this appraisal and this has therefore likely further changed the treatment landscape since this assessment. It is assumed that there will be no patients receiving peg-IFNα + RBV across any genotype and subgroup in which SOF/VEL is recommended by NICE, in line with commissioner estimates based on current notification trends in 2016/2017 as reported in the resource impact template published as part of TA430.[30] However, for GT2 TN NC patients, SOF/VEL is only recommended for patients who are not eligible for IFN. Therefore use of peg-IFNα + RBV is expected to continue in clinical practice at present for GT2 TN NC IFN-eligible patients; this is reflected by its inclusion as the only treatment option for GT2 TN NC IFN-ineligible patients in the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1).[2] This guideline does not recommend peg-IFNα + RBV alone for any other subgroup.

Based on the above considerations, it is reasonable to conclude that peg-IFNα ± RBV alone (i.e. without concomitant use of a DAA) no longer constitutes a meaningful part of clinical practice except in GT2 TN NC IFN-ineligible patients, and hence only represents a comparator to G/P in this appraisal for this specific subgroup.

- **DCV in combination with SOF ± RBV**, is not used in clinical practice in England for patients with GT1 and GT4. This has been confirmed in interviews conducted by AbbVie with clinicians in England, and is reflected by the absence of this treatment as a recommended option for patients with GT1 and GT4 in the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1).[2] Therefore **DCV in combination with SOF without RBV** is only considered a comparator to G/P in this appraisal for GT3 patients, where it is considered in line with the NICE guidance in this genotype.
- **SOF in combination with RBV, ± peg-IFNα,** is not used in clinical practice in England for patients with GT1 and GT4. This has been confirmed in interviews conducted by AbbVie with clinicians in England, and is reflected by the absence of this treatment as a recommended option for patients with GT1 and GT4 in the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1).[2] Therefore **SOF in combination with RBV, ± peg-IFNα** is only considered a comparator to G/P in this appraisal for GT2, GT3, GT5 and GT6 patients, where it is considered in line with the NICE guidance in these genotypes.

With the exception of these therapies highlighted in *grey italic* text in Table 4 and detailed above, the remaining therapies detailed in this table therefore constitute the potential treatments for CHC that constitute part of clinical practice in England. These remaining therapies are therefore all included as comparators to G/P in this appraisal.

As described in Section B.2.13 (Innovation), in the context of the current treatment landscape described above G/P has the potential to simplify the clinical pathway of care in HCV by providing a well-tolerated, once-daily, oral treatment with a short (8 week) treatment duration in a large proportion of patients with HCV (i.e. TN NC patients), an anticipated pan-genotypic marketing authorisation, no requirement for baseline resistance-associated variant (RAV) and viral load testing in patient groups within the anticipated licence, and the potential to remove the requirement for genotyping to make treatment decisions. G/P addresses an unmet need for HCV therapy in several specific CHC patient populations, as recognised by its Promising Innovative Medicine (PIM) status and Early Access to Medicines Scheme (EAMS) designation, including patients with severe renal impairment and specific TE GT3 patients. Finally, in recognition of the

fact that the cost of HCV treatment has a relatively high budget impact, the manufacturer has undertaken to introduce a confidential pricing agreement with NHSE's commissioning medicines unit (CMU).

B.1.5 *Equality considerations*

The use of G/P is not expected to raise any equality issues in current treatment practice. As a pan-genotypic regimen, a recommendation for G/P across the major HCV genotypes may contribute to reduced equality concerns as follows.

G/P is a simple, once-daily, oral regimen with a short treatment duration across all 6 major genotypes in TN NC patients, no requirement for baseline RAV or viral load testing in patient groups within the anticipated licence, and the potential for minimal monitoring. Furthermore, if G/P achieves a positive recommendation in all TN NC subgroups regardless of genotype and IFN-eligibility, all patients in this subgroup within the anticipated licence for G/P would be eligible for an 8-week treatment course of G/P. This therefore has the potential to remove the requirement to genotype any TN NC patients, who represent the majority of patients with HCV,[31] in order to select a NICE-recommended treatment. Taking the above into account, the introduction of G/P may reduce equality issues by providing an opportunity to increasingly provide treatment in community settings (see point 3 in Innovation Section B.2.13) alongside outreach services, improving access to patient populations who have difficulty engaging with secondary care services and adhering to the course of treatment.[32] For example, the provision of CHC treatment in the community is expected to result in improved treatment adherence and therefore better outcomes with lower incidence of hepatic disease particularly among people who inject drugs (PWIDs),[32] patients on opiate substitution therapy, and other chaotic patient populations. The rate of treatment is particularly low amongst PWIDs,[32] but the burden of HCV infection in England and Wales is largely carried by current and ex-PWIDs, [23, 33, 34] so targeting these patients represents the biggest opportunity to prevent onward transmission of HCV infection in England and Wales.[23, 35]

Additionally, there are currently no treatment options with a pan-genotypic licence for CHC patients with severely compromised renal function. G/P has the potential to improve equality of therapeutic access for this patient group, by providing a licensed DAA treatment option.

Finally, despite the approval of SOF/VEL, there remains unmet need for GT2 and GT3 patients. Firstly, SOF/VEL is not recommended by NICE for the treatment of GT2 TN NC patients who are eligible for treatment with IFN. The only therapy available to this subgroup of patients is 24 weeks of peg-IFN + RBV (Table 4). IFN- and RBV-based antiviral treatments are associated with significant side-effects that negatively impact quality of life.[17] G/P offers GT2 TN NC IFN-eligible patients an IFN- and RBV-free treatment option with a substantially shorter treatment duration (8 weeks), providing an opportunity reduce inequalities in access to DAA-based regimens with a short treatment duration in this patient population. Secondly, G/P presents a significant advantage over SOF/VEL for GT3 TN NC patients due to the availability of an 8-week treatment duration. This is of particular importance as GT3 is one of the most prevalent genotypes in the UK and is the predominant strain of infection in South Asian populations, who carry a disproportionately large burden of HCV infection in in North Wales and England.[9, 23, 36] There is inequality amongst this patient population in accessing treatment for CHC due to lack of information and social stigma, making the identification and subsequent treatment of these HCV-infected individuals more challenging.[37] Community-based projects are a proven approach to overcome this barrier.[37] As a treatment that could be provided in the community by pharmacies and other outreach initiatives, G/P provides an opportunity to reduce inequalities in access to treatment amongst this patient population.

B.2 Clinical effectiveness

Summary of clinical effectiveness systematic literature review (SLR)

- A SLR was conducted to identify relevant evidence on the efficacy and safety of G/P and other DAAs that might constitute part of treatment practice for CHC in UK practice.
- Searches of major databases and relevant conference proceedings identified publications for a total of 79 DAA studies, including 7 for G/P: ENDURANCE-1, ENDURANCE-2, ENDURANCE-3, ENDURANCE-4, EXPEDITION-1, SURVEYOR-I and SURVEYOR-II.

Summary of clinical effectiveness

- Between them, the 7 trials for G/P identified by the SLR provide a comprehensive evidence base across a broad patient population with compensated liver disease. This includes both NC and CC patients who are TN and TE, and across all 6 major genotypes, using the dose of 300 mg/120 mg once-daily (OD). These included an active-controlled study (ENDURANCE-3, versus SOF + DCV) and a placebo-controlled study (ENDURANCE-2).
- Across the trial evidence base, 3 different treatment durations (8, 12 and 16 weeks, depending on patient subgroup) were explored; differing treatment durations by patient subgroup are anticipated to be reflected in the marketing authorisation for G/P.
- Overall, across trials presented at licensing and summarised in this submission, G/P achieved an SVR12 rate of [redacted]%, with a virologic failure rate of [redacted]% across 2369 patients.
- Four additional trials outside the scope of the SLR demonstrated the efficacy of G/P treatment in special patient populations: patients with human immunodeficiency virus (HIV) co-infection (EXPEDITON-2), patients with chronic kidney disease (CKD Stage 4/5; EXPEDITION-4), patients who previously failed a DAA-regimen (MAGELLAN-I), and patients treated following liver or renal transplant (MAGELLAN-II). Given the special nature of these populations, these studies did not inform the economic modelling presented in this submission.

Summary of safety

- The registrational clinical programme to confirm the safety and efficacy of G/P includes 6 Phase III studies as well as 2 expanded Phase II studies, totalling >2,300 patients.
- G/P demonstrated a favourable safety profile across the patient populations studied that was similar to placebo and SOF + DCV in the controlled trials.
- Common study drug-related AEs (adverse drug reactions [ADRs]) occurring in ≥5% of patients) were headache, fatigue, and nausea, and were mostly Grade 1 (mild) in severity. Serious ADRs and ADRs leading to premature study drug discontinuation were rare (≤0.1%).
- There were no haematological or blood chemistry findings of concern or considered likely related to treatment. Unlike other currently available protease inhibitors (PIs), no liver-related toxicities and no cases consistent with drug-induced liver injury were identified within the studied patient population.
- The safety of G/P was not affected by fibrosis stage (NC or CC), co-infection with HIV-1, degree of renal insufficiency, or other baseline patient characteristics.

B.2.1 *Identification and selection of relevant studies*

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

B.2.2 *List of relevant clinical effectiveness evidence*

The SLR identified 7 trials of G/P for which published literature was available, as follows:

- ENDURANCE-1
- ENDURANCE-2
- ENDURANCE-3
- ENDURANCE-4
- EXPEDITION-1
- SURVEYOR-I
- SURVEYOR-II

In addition, information on 4 further clinical trials of G/P in patients with CHC is included this submission (EXPEDITION-2, EXPEDITION-4, MAGELLAN-I, MAGELLAN-II). These trials were conducted in special populations of patients with HIV co-infection, renal impairment, failure on prior DAAs and a post-transplant population, respectively. The results from these trials have been published,[5, 38-43] but were not identified by the SLR as trials in special populations were excluded under the SLR eligibility criteria (see Appendix D). These studies provide supportive data for the submission; however, whilst EXPEDITION-4 and MAGELLAN-I are presented in full, limited information is presented for EXPEDITION-2 and MAGELLAN-II as these trials have only recently been completed.

The G/P registrational programme included a broad patient population with compensated liver disease (NC and CC) across all major genotypes using the dose of 300 mg/120 mg. TN patients and patients with previous experience with any combination of peg-IFN, RBV, SOF, NS5A inhibitors, or PIs were permitted to enrol in the clinical trial programme, with specific inclusion criteria varied between the individual studies (see below for details). In addition, studies within the programme enrolled special populations of patients as described above.

Table 5 describes the treatment duration for the **anticipated** licence for G/P. In the sections that follow (both efficacy and safety), the entire G/P registrational programme is described (not limited to those trials in which patients were treated in line with the anticipated licence) to demonstrate the consistency of treatment effect with G/P.

Table 5: Treatment duration for anticipated licence (not yet confirmed)

Patient population	NC	CC
TN	8 weeks for all genotypes	12 weeks for all genotypes
TE, previously treated with: • Peg-IFN + RBV • SOF + peg-IFN + RBV	GT1,2, 4–6: 8 weeks GT3: 16 weeks	GT1, 2, 4–6: 12 weeks GT3: 16 weeks

• SOF + RBV		

Abbreviations: CC, compensated cirrhosis; GT, genotype; NC, non-cirrhotic; peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve

Studies in TN NC patients explored 8- and 12-week treatment durations. Among GT1-, GT2-, and GT3-infected NC patients, efficacy comparisons between 8- and 12-week durations were performed through non-inferiority analyses (either between study arms or against a fixed SVR threshold based on historical data). The programme included one registrational study with an active-controlled design for GT3 using SOF + DCV. Among GT4-, GT5-, and GT6-infected NC patients, descriptive statistical efficacy comparisons between durations were performed given the lower prevalence and thus smaller sample sizes for these genotypes. The programme also included a placebo-controlled design in one registrational study to characterise the safety of the regimen.

Studies in CC patients were conducted using a 12-week duration of treatment across patients infected with GT1, GT2, and GT4–6 and 12- or 16-week duration in GT3-infected patients (12 weeks [TN] and 16 weeks [TE]).

NC and CC subjects who failed a previous regimen containing an NS5A/B inhibitor and/or an NS3/4A PI were treated for 12 or 16 weeks in one study. Finally, patients CKD Stage 4/5 infected with any of the major genotypes were included in EXPEDITION-4 with a treatment duration of 12 weeks.

In addition to registrational studies, treatment arms from supportive Phase II studies using the regimen selected for registrational studies were pooled with arms from the registrational studies for some analyses of efficacy and safety.

A summary of the trials providing evidence for G/P is provided in Table 6 to Table 9 below.

Table 6: Clinical effectiveness evidence: ENDURANCE trials

Study	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
Study design	Multicentre, randomised, open-label, Phase III	Multicentre, randomised, double-blind, placebo-controlled, Phase III	Multicentre, randomised, open-label, active-controlled, Phase III	Multicentre, open-label, single-arm, Phase III
Population	• GT1 • TN or TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN (TE-PRS) • NC • With or without HIV-1 co-infection	• GT2 • TN or TE-PRS • NC	• GT3 • TN • NC	• GT4, GT5 or GT6 • TN or TE-PRS • NC
Intervention(s)	G/P (300 mg/120 mg OD) for 8 or 12 weeks	G/P (300 mg/120 mg OD) for 12 weeks	G/P (300 mg/120 mg OD) for 8 or 12 weeks	G/P (300 mg/120 mg OD) for: 12 weeks
Comparator(s)	None	Placebo	SOF + DCV for 12 weeks	None
Indicate if trial supports application for marketing authorisation	Yes	No	Yes	No
Indicate if trial used in the economic model	Yes	No	Yes	No
Rationale for use/non-use in the model	Key data for GT1 TN and TE NC patients treated with G/P for 8 weeks with the licensed dose	Treatment duration not in line with anticipated licence for NC patients	Key data for GT3 TN NC patients treated with G/P for 8 weeks with the licensed dose	Treatment duration not in line with anticipated licence for NC patients
Reported outcomes specified in the decision problem	• Mortality • SVR	• Mortality • SVR	• Mortality • SVR	• Mortality • SVR

Study	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
	• Development of resistance to treatment • AEs • HRQoL	• Development of resistance to treatment • AEs • HRQoL	• Development of resistance to treatment • AEs • HRQoL	• Development of resistance to treatment • AEs • HRQoL
All other reported outcomes	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics

Abbreviations: AE, adverse event; DCV, daclatasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IFN, interferon; LLOQ, lower limit of quantitation; NC, non-cirrhotic; OD, once daily; Peg-IFN, pegylated IFN; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-PRS, TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

Table 7: Clinical effectiveness evidence: EXPEDITION-1 and SURVEYOR-II, Parts 2 and 3

Study	M14-172 (EXPEDITION-1)[56, 57]	M14-868 (SURVEYOR-II, Part 2)[58-64]	M14-868 (SURVEYOR-II, Part 3)[59, 63-65]
Study design	Multicentre, open-label, single-arm, Phase III	Multicentre, partially-randomised open-label, Phase II	
Population	• GT1, GT2, GT4, GT5 or GT6 • TN or TE-PRS	• GT2, GT3 • TN or TE with regimens containing peg-IFN/RBV (TE-PR)	• GT3 • TN CC

Study	M14-172 (EXPEDITION-1)[56, 57]	M14-868 (SURVEYOR-II, Part 2)[58-64]	M14-868 (SURVEYOR-II, Part 3)[59, 63-65]
	• CC	• NC or CC (GT3 CC were TN only[a]; GT2 were NC only)	• TE-PRS NC CC
Intervention(s)	G/P (300 mg/120 mg OD) for 12 weeks	G/P (300 mg/120 mg OD) for 8 or 12 weeks ± RBV	G/P (300 mg/120 mg OD) for 12 or 16 weeks
Comparator(s)	None		
Indicate if trial supports application for marketing authorisation	Yes	Yes	No
Indicate if trial used in the economic model	Yes	Yes, pooled with data from the same subpopulation of patients and treatment dose and duration from Part 3	Yes For GT3 TN and TE CC, pooled with data from the same subpopulation of patients and treatment dose and duration from Part 2
Rationale for use/non-use in the model	Key data for GT1, GT2, GT4, GT5 and GT6 TN and TE CC patients treated with G/P for 12 weeks with the licensed dose	Key data for GT3 TN CC patients treated with G/P for 12 weeks with the licensed dose, and GT3 TE CC patients treated with G/P for 16 weeks with the licensed dose	Key data for GT3 TN CC patients treated with G/P for 12 weeks with the licensed dose, and GT3 TN and TE NC patients treated with G/P for 16 weeks with the licensed dose
Reported outcomes specified in the decision problem	• Mortality • SVR • Development of resistance to treatment • AEs • HRQoL	• Mortality • SVR • Development of resistance to treatment • AEs • HRQoL	• Mortality • SVR • Development of resistance to treatment • AEs • HRQoL
All other reported outcomes	• On-treatment virologic failure	• On-treatment virologic failure	• On-treatment virologic failure

Study	M14-172 (EXPEDITION-1)[56, 57]	M14-868 (SURVEYOR-II, Part 2)[58-64]	M14-868 (SURVEYOR-II, Part 3)[59, 63-65]
	• Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics

[a]When SURVEYOR-II, Part 2 enrolment was initiated, both TN and TE-PR CC GT3-infected patients were eligible for enrolment, but after 7 TE-PR CC GT3-infected patients were enrolled, enrolment was halted for these patients based on feedback from the United States Food and Drug Administration.
Abbreviations: AE, adverse event; CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HRQoL, health-related quality of life; IFN; interferon; LLOQ, lower limit of quantitation; NC, non-cirrhotic; OD, once daily; peg-IFN, pegylated IFN; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-PR, TE with regimens containing peg-IFN/RBV; TE-PRS, TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

Table 8: Clinical effectiveness evidence: SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 trials

Study	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66-68]	M14-868 (SURVEYOR-II, Part 1)[59, 60, 63, 64, 69]	M14-868 (SURVEYOR-II, Part 4)[59, 63, 64, 70]
Study design	Multicentre, open-label, Phase II	Multicentre, randomised, open-label, Phase II	Multicentre, open-label, single-arm, Phase II
Population	• GT1, GT4, GT5 or GT6 • TN or TE-PR • GT1 NC and CC; GT4, GT5 and GT6 NC only	• GT2, GT3 • TN or TE-PR • NC	• GT2, GT4, GT5 or GT6 • TN or TE-PRS • NC
Intervention(s)	G/P (300 mg/120 mg OD) for 8 or 12 weeks	G/P (300 mg/120 mg OD or 200mg/120 mg OD) for 12 weeks ± RBV	G/P (300 mg/120 mg OD) for 8 weeks
Comparator(s)	None		
Indicate if trial supports application for marketing authorisation	No	No	Yes

Study	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66-68]	M14-868 (SURVEYOR-II, Part 1)[59, 60, 63, 64, 69]	M14-868 (SURVEYOR-II, Part 4)[59, 63, 64, 70]
Indicate if trial used in the economic model	No	Yes, pooled with data from the same subpopulation of patients and treatment dose and duration from Part 4	Yes For GT2, pooled with data from the same subpopulation of patients and treatment dose and duration from Part 1
Rationale for use/non-use in the model	Data from larger trials were available to inform the economic model inputs for GT1 TN and TE-PR NC patients treated with G/P for 8 weeks, and from GT1 TN and TE-PR CC patients treated with G/P for 12 weeks	Key data for GT2 TN and TE NC patients treated with G/P for 8 weeks with the licensed dose	Key data for GT2, GT4, GT5 and GT6 TN and TE NC patients treated with G/P for 8 weeks with the licensed dose
Reported outcomes specified in the decision problem	• Mortality • SVR • Development of resistance to treatment • AEs • HRQoL	• Mortality • SVR • Development of resistance to treatment • AEs • HRQoL	• Mortality • SVR • Development of resistance to treatment • AEs • HRQoL
All other reported outcomes	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics

Abbreviations: AE, adverse event; CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HRQoL, health-related quality of life; IFN, interferon; LLOQ, lower limit of quantitation; NC, non-cirrhotic; peg-IFN, pegylated IFN; OD, once daily; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-PR, TE with regimens containing peg-IFN/RBV; TE-PRS, TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

Table 9: Clinical effectiveness evidence: EXPEDITION-4 and MAGELLAN-I trials

Study	M15-462 (EXPEDITION-4)[38, 71, 72]	M15-410 (MAGELLAN-I, Part 1) [5, 39, 73, 74]	M15-410 (MAGELLAN-I, Part 2) [5, 40, 41, 73, 74]
Study design	Multicentre, open-label, single-arm, Phase III	Multicentre, randomised, open-label, Phase II	
Population	• GT1, GT2, GT3, GT4, GT5 or GT6 • TN (all genotypes) or TE-PRS (GT1, GT2, GT4, GT5 or GT6) • NC or CC • Who had severe renal impairment or end-stage renal disease (including those on dialysis)	• GT1 • TE-DAA • NC Note that this patient population is not within the anticipated licence for G/P	• GT1, GT4, GT5 or GT6 • TE-DAA • NC or CC Note that this patient population is not within the anticipated licence for G/P
Intervention(s)	G/P (300 mg/120 mg OD) for 12 weeks	G/P (300 mg/120 mg OD) for 12 weeks ± RBV	G/P (300 mg/120 mg OD) for 12 or 16 weeks
Comparator(s)	None		
Indicate if trial supports application for marketing authorisation	No	No	Yes
Indicate if trial used in the economic model	No	No	No
Rationale for use/non-use in the model	The submission already considers an extensive number of subgroup subdivided by genotype, treatment history and cirrhosis status. A subgroup analysis for patients with severe renal impairment was therefore not performed in order to focus the decision problem on subgroups that are historically considered important in previous NICE treatment recommendations. Additionally, the patient population studied in MAGELLAN-I is not within the anticipated licence for G/P.		
Reported outcomes specified in the decision problem	• Mortality • SVR • Development of resistance to treatment • AEs	• Mortality • SVR • Development of resistance to treatment • AEs	• Mortality • SVR • Development of resistance to treatment • AEs

Study	M15-462 (EXPEDITION-4)[38, 71, 72]	M15-410 (MAGELLAN-I, Part 1) [5, 39, 73, 74]	M15-410 (MAGELLAN-I, Part 2) [5, 40, 41, 73, 74]
	• HRQoL		
All other reported outcomes	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics	• On-treatment virologic failure • Post-treatment relapse • Percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • Pharmacokinetics

Abbreviations: AE, adverse event; CC, compensated cirrhosis; DAA, directly-acting antiviral; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HRQoL, health-related quality of life; IFN, interferon; LLOQ, lower limit of quantitation; NC, non-cirrhotic; peg-IFN, pegylated IFN; OD, once daily; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-DAA, TE with regimens containing DAAs; TE-PRS, TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

EXPEDITION-2 was a multicentre, open-label Phase III trial that enrolled NC and CC patients with HIV co-infection across all major genotypes. MAGELLAN-II was a multicentre, open-label, single-arm Phase III trial that enrolled NC patients across all genotypes who had received a liver or renal transplant. Patients were TN or, with the exception of GT3 patients, TE. Only limited details are presented for these 2 trials, which have only recently been completed. EXPEDITION-4, MAGELLAN-I, Part 1 and MAGELLAN-I, Part 2, which are included in Sections 2.2 to 2.6, were also performed in special patient populations. None of these studies were included in the economic model because it is not considered relevant to perform separate economic analyses in these specific subpopulations. In addition, the subpopulation studied in MAGELLAN-I is not line with the anticipated licence for G/P (see Section B.3 for further details).

ENDURANCE-2 and ENDURANCE-4 were not used to populate the economic model but are included in Sections 2.2 to 2.6. The results of these large registrational Phase III studies support the consistent efficacy of G/P so it was considered relevant to present these as supporting studies. These studies were not included in the economic model because the treatment duration does not align with the **anticipated** licence.

SURVEYOR-I, Part 2 was not used to populate the economic model but is included in Sections 2.2 to 2.6. The results of this study are presented as a supporting early Phase II study within the clinical development programme. This study was not included in the economic model because results for larger studies that also align with the **anticipated** licence were available (see Section B.3 for further details).

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

B.2.3.1 Comparative summary of trial methodology

As noted above, the combination treatment regimen of once-daily G/P (as co-formulated tablets) was developed for use in TN and TE HCV GT1- to GT6-infected NC and CC patients. The clinical trial programme for G/P provides an evidence base across all 6 major genotypes, as summarised in Table 10. The clinical trial programme also investigates the use of G/P in specific subgroups of patients within these populations: patients with CKD Stage 4/5, patients co-infected with HIV-1, patients who have previously failed a DAA-containing (NS5A/B inhibitor and/or an NS3/4A PI) regimen, and patients treated in the post-liver or post-renal transplant setting. Neither Table 10 nor the methodology sections that follow include two trials in Japanese patients with CHC, CERTAIN-1 and CERTAIN-2, because the fact that these two trials were conducted entirely in Japanese patients precludes their generalisability to the UK patient population and subsequently their use in the economic model. The details of these trials can be found in Section B.2.4.2.5.

Table 10. Matrix of trial evidence by genotype, cirrhosis and treatment status (including relevant registrational Phase II data)

Genotype	NC		CC	
	TN	TE	TN	TE
1	**Primary Phase III study:** **ENDURANCE-1 (includes HIV/HCV)** Further evidence: SURVEYOR-I, Part 2 EXPEDITION-4 (subgroup: CKD) EXPEDITION-2 (subgroup: HIV/HCV) MAGELLAN-2 (subgroup: PLT/PKT)	**Primary Phase III study:** **ENDURANCE-1 (includes HIV/HCV)** Further evidence: SURVEYOR-I, Part 2 EXPEDITION-4 (subgroup: CKD) MAGELLAN-1, Parts 1 and 2 (subgroup: DAA failures[a]) EXPEDITION-2 (subgroup: HIV/HCV) MAGELLAN-2 (subgroup: PLT/PKT)	**Primary Phase III study:** **EXPEDITION-1** Further evidence: EXPEDITION-4 (subgroup: CKD) EXPEDITION-2 (subgroup: HIV/HCV)	**Primary Phase III study:** **EXPEDITION-1** Further evidence: EXPEDITION-4 (subgroup: CKD) MAGELLAN-1, Part 2 (subgroup: DAA failures[a]) EXPEDITION-2 (subgroup: HIV/HCV)
2	**Primary Phase III study:** **ENDURANCE-2** **Key registrational trials:** **SURVEYOR-II, Part 4 (8-week duration)** Further evidence: SURVEYOR-II, Part 1 SURVEYOR-II, Part 2 EXPEDITION-4 (subgroup: CKD) EXPEDITION-2 (subgroup: HIV/HCV) MAGELLAN-2 (subgroup: PLT/PKT)	**Primary Phase III study:** **ENDURANCE-2** **Key registrational trials:** **SURVEYOR-II, Part 4 (8-week duration)** Further evidence: SURVEYOR-II, Part 1 SURVEYOR-II, Part 2 EXPEDITION-4 (subgroup: CKD) EXPEDITION-2 (subgroup: HIV/HCV) MAGELLAN-2 (subgroup: PLT/PKT)	**Primary Phase III study:** **EXPEDITION-1** Further evidence: EXPEDITION-4 (subgroup: CKD) EXPEDITION-2 (subgroup: HIV/HCV)	**Primary Phase III study:** **EXPEDITION-1** Further evidence: EXPEDITION-4 (subgroup: CKD) EXPEDITION-2 (subgroup: HIV/HCV)
3	**Primary Phase III study:** **ENDURANCE-3** **Key registrational trials:** **SURVEYOR-II, Part 3** Further evidence: SURVEYOR-II, Part 1	**Registrational trials:** **SURVEYOR-II, Part 3** Further evidence: SURVEYOR-II, Part 1 SURVEYOR-II, Part 2 EXPEDITION-4 (subgroup: CKD)	**Registrational trials:** **SURVEYOR-II, Part 3** SURVEYOR-II, Part 2 EXPEDITION-4 (subgroup: CKD) EXPEDITION-2 (subgroup: HIV/HCV)	**Registrational trials:** **SURVEYOR-II, Part 3**

Genotype	NC		CC	
	TN	TE	TN	TE
	SURVEYOR-II, Part 2 EXPEDITION-4 (subgroup: CKD) EXPEDITION-2 (subgroup: HIV/HCV) MAGELLAN-2 (subgroup: PLT/PKT)	EXPEDITION-2 (subgroup: HIV/HCV) MAGELLAN-2 (subgroup: PLT/PKT)		
4, 5 or 6	**Primary Phase III study:** **ENDURANCE-4** **Key registrational trials:** **SURVEYOR-II Part 4 (8-week duration)** Further evidence: SURVEYOR-I, Part 2 EXPEDITION-4 (subgroup: CKD) EXPEDITION-2 (subgroup: HIV/HCV) MAGELLAN-2 (subgroup: PLT/PKT)	**Primary Phase III study:** **ENDURANCE-4** **Key registrational trials:** **SURVEYOR-II, Part 4 (8-week duration)** Further evidence: SURVEYOR-I, Part 2 EXPEDITION-4 (subgroup: CKD) MAGELLAN-1, Part 2 (subgroup: DAA failures[a]) EXPEDITION-2 (subgroup: HIV/HCV) MAGELLAN-2 (subgroup: PLT/PKT)	**Primary Phase III study:** **EXPEDITION-1** Further evidence: EXPEDITION-4 (subgroup: CKD) EXPEDITION-2 (subgroup: HIV/HCV)	**Primary Phase III study:** **EXPEDITION-1** Further evidence: EXPEDITION-4 (subgroup: CKD) MAGELLAN-1, Part 2 (subgroup: DAA failures[a]) EXPEDITION-2 (subgroup: HIV/HCV)

[a]This patient subgroup is not included in the anticipated licence for G/P. DAA-containing regimens are defined as follows. In Part 1: including, but not limited to, DCV + SMV, DCV + SOF, ASV + DCV, SOF + SMV and OBV/PTV/RTV. In Part 2: consisting of NS5A-inhibitors DCV, LDV, or OBV, and/or NS3/4A PIs PTV/RTV, SMV, TVR, or BOC, with or without IFN and/or RBV

Note: Trials have been listed in the relevant section of the matrix only if a treatment arm with a dose of G/P (300 mg/120 mg) was included for that particular population (regardless of treatment duration or combination with RBV)

Abbreviations: ASV, asunaprevir; BOC, boceprevir; CC, compensated cirrhosis; CKD, chronic kidney disease; DAA, direct-acting antiviral; DCV, daclatasvir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; IFN, interferon; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; RTV, ritonavir; SOF, sofosbuvir; SMV, simeprevir; TE, treatment-experienced; TN, treatment-naïve; PIs, protease-inhibitors; PKT, post-kidney transplant; PLT, post-liver transplant; RBV, ribavirin; TVR, telaprevir;

Although specific study outcomes differed among trials, across all trials SVR12 (sustained virologic response; defined as HCV RNA less than the lower limit of quantitation [LLOQ] at 12 weeks after the end of treatment [EOT]) was the measure of the primary outcome, and on-treatment virologic failure and post-treatment relapse (12 weeks after end of treatment) were secondary outcomes. Additional outcomes frequently specified included the percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period, SVR4 (defined as HCV RNA less than LLOQ at 4 weeks after EOT), SVR24 (defined as HCV RNA less than LLOQ at 24 weeks after EOT), the percentage of patients who relapsed after achieving SVR12, next generation sequencing to identify HCV variants at signature amino acid positions, pharmacokinetics and patient reported outcomes. Pharmacokinetic outcomes, although measured in the studies, are not presented in this submission.

Comparisons conducted for the primary efficacy endpoint analyses were performed against an active control, historical controls, or across study arms with different treatment durations of G/P. A single, active comparator or historical control could not be employed across the registrational studies since, at the time of study conduct, there was no single regimen that was approved across all HCV genotypes.

One trial (ENDURANCE-3) included an active comparator arm (SOF + DCV for 12 weeks); this comparator is relevant for GT3 infection – the patient genotype enrolled in ENDURANCE-3. One trial (ENDURANCE-2) also included a placebo arm which crossed over to active treatment after 12 weeks.

In three trials (ENDURANCE-1 and -2 and SURVEYOR-II, Part 4), the SVR12 rate achieved with G/P treatment was compared to historical SVR12 rates of the current standard of care (SoC). For ENDURANCE-1, which recruited GT1 patients, G/P treatment was compared to OBV/PTV/RTV + DSV ± RBV or SOF/LDV for 12 weeks – both of which are relevant comparators for GT1. For the GT2 patients enrolled in ENDURANCE-2 (which recruited GT2 patients only) and SURVEYOR-II, Part 4 (which recruited GT2 patients to some treatment arms), G/P treatment was compared to SOF + RBV for 12 weeks, which is a relevant comparator for GT2.

The use of single arm and historically-controlled trials in the treatment of HCV is common and a result of the features of both the disease and existing treatments:

- Historical controls: in genotypes with existing established DAA options, SVR rates for the current SoC therapies at the time of the trials in TN and TE NC patients were well established and very high (≥95%), therefore historical control data were used to provide a comparator for assessment of efficacy
- Single-arm trials: such designs were considered appropriate in the context of expecting a very high SVR rate with a rate of virologic failure less than 5%, diminishing the need for an active-controlled design, and are widely used in HCV. Furthermore, for many multi-genotypic trials there was no single SoC treatment for all genotypes recruited into the trials
- Placebo-controlled trials: from a safety standpoint, the implementation of a placebo-controlled design was considered challenging in HCV patients with CC in those studies that included these patients, because of the perceived greater risk of progression to DCC with treatment delays for a placebo group in some countries where trials were conducted

The methodologies and study designs of the relevant trials are summarised briefly in Sections B.2.3.2 to B.2.3.4 and in more detail in B.2.3.5 to B.2.3.8.

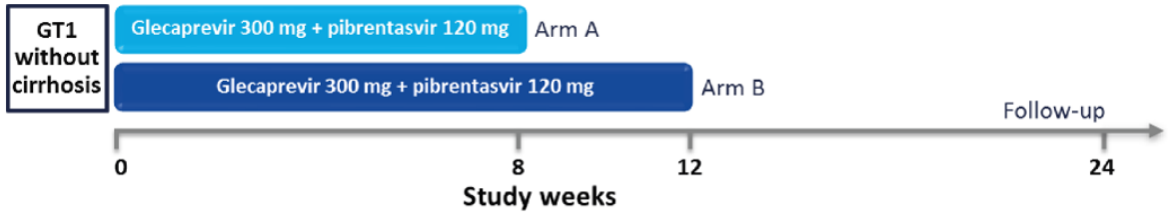
B.2.3.2 ENDURANCE trials

The ENDURANCE trials are the key studies for NC patients and provide evidence across all 6 major genotypes. ENDURANCE-1, ENDURANCE-2 and ENDURANCE-4 recruited both TN and TE patients; ENDURANCE-3 recruited TN patients only. All four trials were multicentre Phase III trials. ENDURANCE-1, ENDURANCE-2 and the 12-week treatment arms of ENDURANCE-3 were randomised. ENDURANCE-1, 3, and 4 were open-label. ENDURANCE-2 was double-blind and placebo-controlled, and ENDURANCE-3 was active-controlled.

ENDURANCE-1 and ENDURANCE-3 provide key evidence for the 8-week treatment duration for G/P in NC GT1 and GT3 patients. Additionally, the SURVEYOR-II, Part 4 study (described in Section B.2.3.3) is a Phase II registrational study that provides key evidence for the 8-week treatment duration in NC GT2 and GT4–6 patients. This study is therefore considered a key, rather than supportive, study in these populations. Finally, clinical evidence in GT3 TE NC patients is provided by the registrational Phase II trial SURVEYOR-II, Part 3, described in Section B.2.3.3.

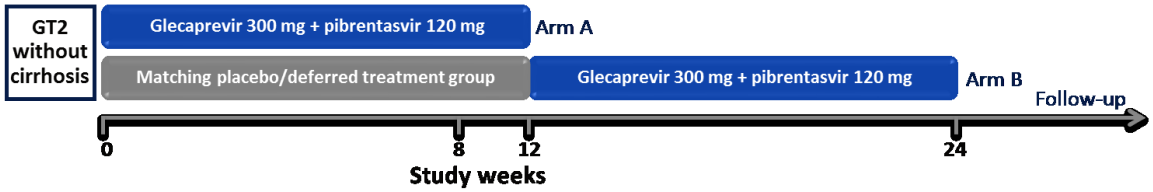
The study designs for the ENDURANCE trials are described in Figure 1 to Figure 4.

Figure 1: Study design for ENDURANCE-1



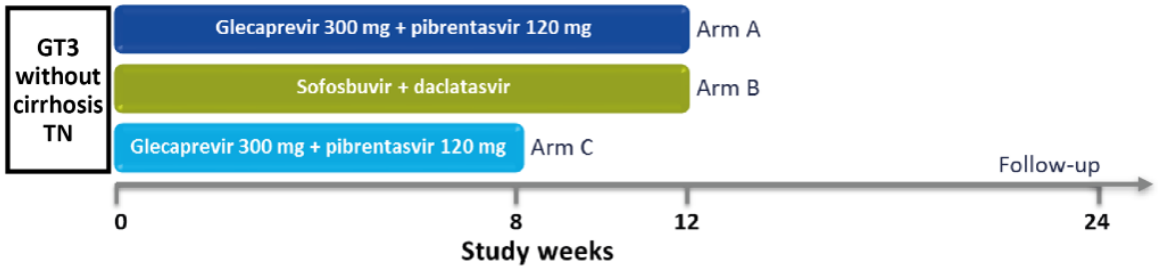
Abbreviations: GT, genotype

Figure 2: Study design for ENDURANCE-2



Abbreviations: GT, genotype

Figure 3: Study design for ENDURANCE-3



Abbreviations: GT, genotype; TN, treatment-naïve

Figure 4: Study design for ENDURANCE-4

Abbreviations: GT, genotype

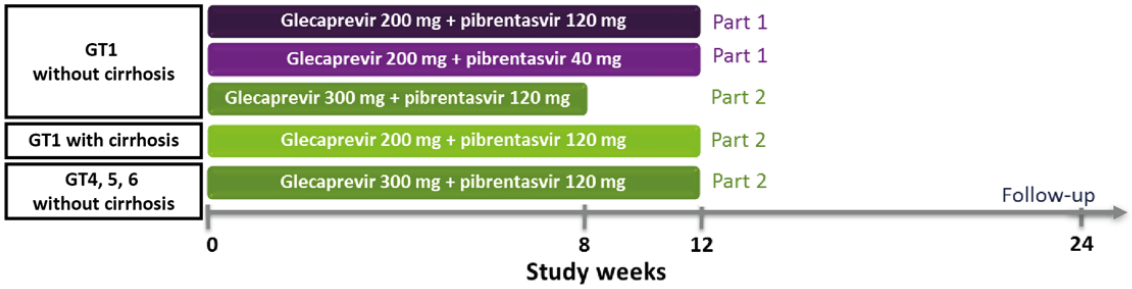
B.2.3.3 EXPEDITION-1, SURVEYOR-I and SURVEYOR-II trials

The EXPEDITION-1 study is the key study providing evidence in CC patients across GT1, GT2 and GT4–6. The study was a multicentre, open-label, single-arm, Phase III trial. For GT3 CC patients, the registrational Phase II study SURVEYOR-II, Part 3 provides the key evidence base (although it should be noted that this study also provides evidence in NC patients with GT3 infection). Additional supportive evidence in GT3 CC patients is provided by the non-registrational, Phase II study SURVEYOR-II, Part 2, which also provides supportive evidence in the NC population. SURVEYOR-II Parts 2 and 3 were multicentre-, partially-randomised, open-label studies. As the three studies providing evidence in CC patients, the methodology of these three studies is summarised together in Section B.2.3.6. Data are only presented for trial arms using the licensed dose of G/P (300 mg/120 mg) without RBV.

SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 provide evidence in NC patients only (one arm in SURVEYOR-I, Part 2 included CC patients, but this was a dose of G/P outside of the proposed licence and is therefore not considered further). SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 were multicentre, open-label Phase III studies. SURVEYOR-II, Part 1 was a randomised study, whereas SURVEYOR-II, Part 4 was a single-arm study. The evidence from the SURVEYOR-I, Part 2 and SURVEYOR-II, Part 1 studies in NC patients is considered supportive to that provided by the ENDURANCE studies, because these are non-registrational Phase II studies, whereas the ENDURANCE studies are Phase III, registrational studies. SURVEYOR-II, Part 4 is a registrational Phase II trial. The patient populations investigated in this trial (NC patients with GT2 infection, and NC patients with GT4–6 infection) were also investigated in the Phase III ENDURANCE-2 and ENDURANCE-4 trials, respectively. However, the SURVEYOR-II, Part 4 study is a registrational study and provides key evidence for the 8-week treatment duration in GT2 and GT4–6. This study is therefore considered a key, rather than supportive, study in these populations.

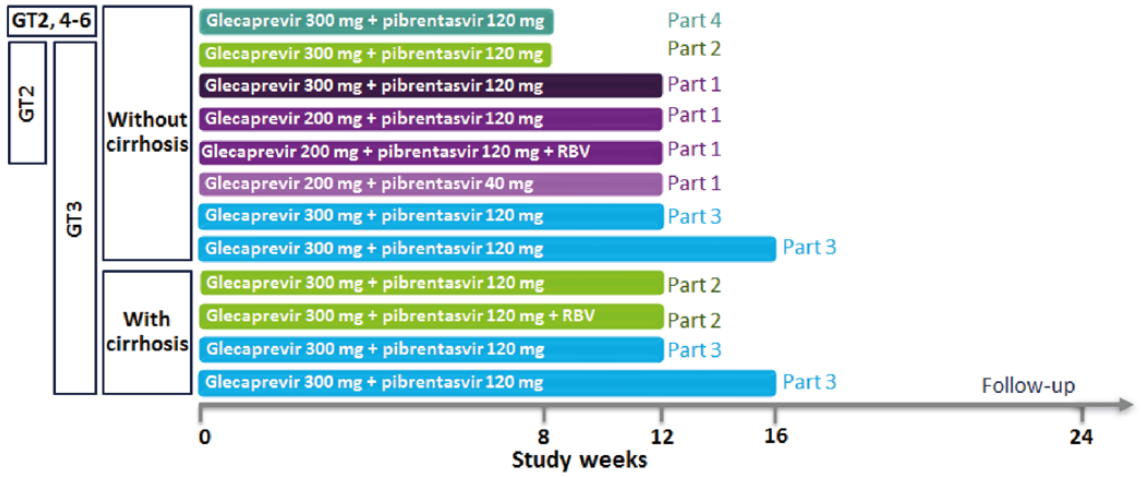
The study designs for these trials are described in Figure 5 to Figure 7.

Figure 5: Study design for SURVEYOR-I



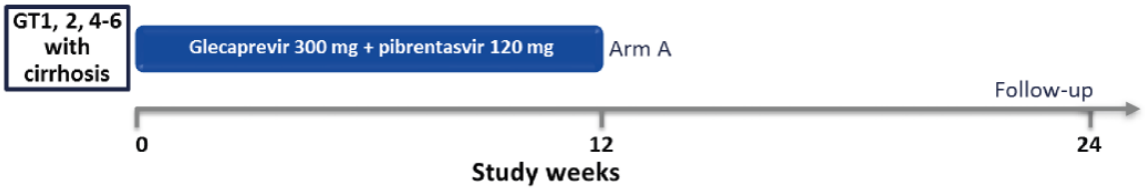
Abbreviations: GT, genotype

Figure 6: Study design for SURVEYOR-II



Abbreviations: GT, genotype; RBV, ribavirin

Figure 7: Study design for EXPEDITION-1



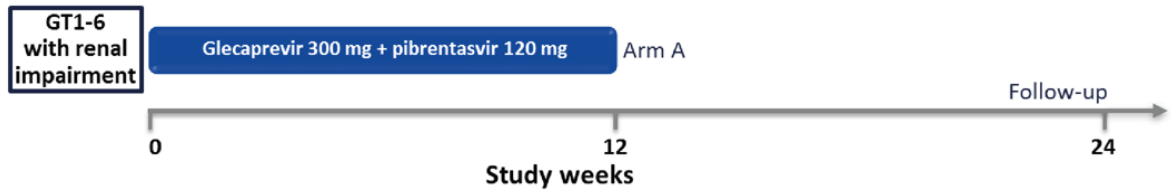
Abbreviations: GT, genotype

B.2.3.4 EXPEDITION-2, EXPEDITION-4, MAGELLAN-I and MAGELLAN-II trials

These studies were performed in special patient populations. EXPEDITION-4 was a multicentre, open-label, single-arm, Phase II trial that enrolled NC and CC patients with renal impairment across all major genotypes. MAGELLAN-I was a multicentre, randomised, open-label, Phase II trial that enrolled patients who had previously failed a prior anti-HCV DAA-containing regimen. MAGELLAN-I, Part 1 enrolled GT1-infected NC patients, whereas MAGELLAN-I, Part 2 enrolled NC and CC patients with GT1, GT4, GT5 or GT6 infection. Data are only presented for trial arms using the licensed dose of G/P (300 mg/120 mg) without RBV.

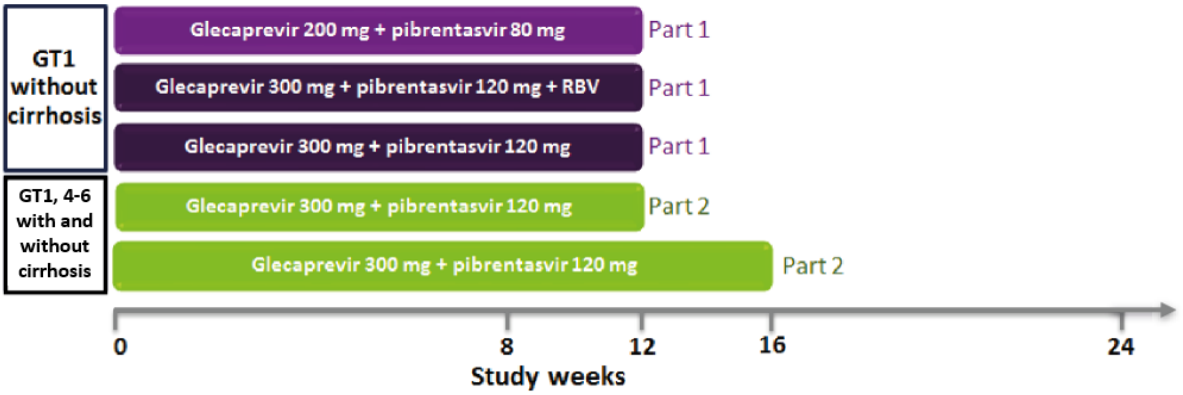
The study designs for EXPEDITION-4 and MAGELLAN-I are described in Figure 8 and Figure 9, respectively.

Figure 8: Study design for EXPEDITION-4



Abbreviations: GT, genotype

Figure 9: Study design for MAGELLAN-I

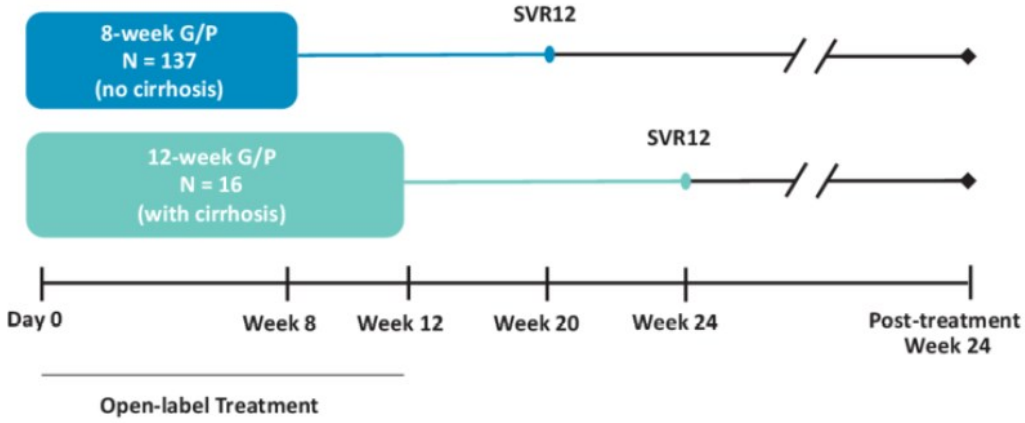


Abbreviations: GT, genotype

EXPEDITION-2 was a multicentre, open-label Phase III trial that enrolled NC and CC patients with HIV co-infection across all major genotypes. MAGELLAN-II was a multicentre, open-label, single-arm Phase III trial that enrolled NC patients across all genotypes who had received a liver or renal transplant. Patients were TN or, with the exception of GT3 patients, TE. Only limited details are presented for these two trials, which have only recently been completed.

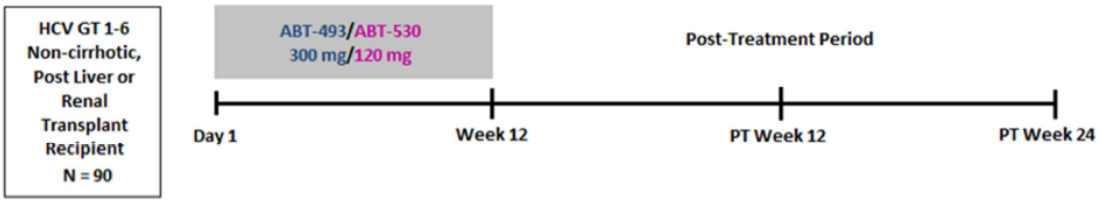
The study designs for EXPEDITION-2 and MAGELLAN-II are described in Figure 10 and Figure 11, respectively.

Figure 10: Study design for EXPEDITION-2



Abbreviations: G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; SVR, sustained virologic response

Figure 11: Study design for MAGELLAN-II



N is approximate
Abbreviations: GT, genotype; HCV, hepatitis C virus; PT, post-treatment

B.2.3.5 ENDURANCE trials

Table 11: Comparative summary of methodology: ENDURANCE trials

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
Clinicaltrials.gov identifier	NCT02604017	NCT02640482	NCT02640157	NCT02636595
Study population	• GT1 • TN or TE-PRS • NC • With or without HIV-1 co-infection • G/P treatment length: 8 or 12 weeks	• GT2 • TN or TE-PRS • NC • G/P treatment length: 12 weeks	• GT3 • TN • NC • G/P treatment length: 8 or 12 weeks	• GT4, GT5 or GT6 • TN or TE-PRS • NC • G/P treatment length: 12 weeks
Study objective	• To compare the efficacy of 8- versus 12-week treatment with G/P, in TN or TE-PRS patients without cirrhosis as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of each treatment regimen	• To compare the efficacy of 12-week treatment with G/P versus the historical efficacy of 12-week treatment with SOF + RBV, in TN or TE-PRS patients without cirrhosis as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of 12-week treatment with G/P compared to placebo	• To compare the efficacy of 12-week treatment with G/P versus 12-week treatment with SOF + DCV and versus 8-week treatment with G/P, in TN patients without cirrhosis as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of 12-week treatment with G/P compared to 12-week	• To evaluate the efficacy of 12-week treatment with G/P in TN or TE-PRS patients without cirrhosis as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of the treatment regimen

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
			treatment with SOF + DCV	
Location	110 study locations in the United States, Australia, Austria Belgium, Canada, Chile, France, Germany, Hungary, Israel, Italy, Korea, Lithuania, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Spain, Sweden, Switzerland and Taiwan, and 6 sites (28 patients) in the United Kingdom	55 study locations in the United States, Belgium, France, Italy, Korea, Lithuania, Portugal and Taiwan	69 study locations in the United States, Australia, Canada, France, Germany, New Zealand, Sweden and Switzerland, and 9 sites (81 patients) in the United Kingdom	25 study locations in Belgium, Canada, France, Italy, Portugal, Spain and South Africa, and 6 sites (18 patients) in the United Kingdom
Trial design	Multicentre, randomised, open-label, Phase III	Multicentre, randomised, double-blind, placebo-controlled, Phase III	Multicentre, partially randomised, open-label, active-controlled, Phase III	Multicentre, open-label, single-arm, Phase III
Method of randomisation	An IRT system was employed to manage drug dispensation and compliance, and (where applicable) patient randomisation and treatment assignment			
	Randomisation was stratified by: • Screening viral load (< or ≥6 million IU/mL) • HCV GT1 subtype (1b or non-1b)	Randomisation was stratified by type of previous treatment experience: • TN • TE with either IFN, peg-IFN ± RBV or SOF + RBV ± peg-IFN		
Duration of study	Treatment duration: 8 or 12 weeks depending on treatment assignment	Treatment duration: 12 or 24 weeks depending on treatment assignment	Treatment duration: 8 or 12 weeks depending on treatment assignment	Treatment duration: 12 weeks

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
	Follow-up: up to 24 weeks post-treatment	Follow-up: up to 24 weeks post-treatment	Follow-up: up to 24 weeks post-treatment	Follow-up: up to 24 weeks post-treatment
Settings and locations where data were collected	Data were collected at the trial sites listed above			
Intervention(s) (n=) and comparators(s) (n=)	Patients receiving G/P received three fixed-dose combination tablets containing 100 mg of GLE and 40 mg of PIB OD Patients were randomised in a 1:1 ratio to: • G/P for 12 weeks (n=352) • G/P for 8 weeks (n=351)	In the DB treatment period, patients were randomised in a 2:1 ratio to: • G/P for 12 weeks (n=202) • Placebo for 12 weeks (n=100) In the OL treatment period, patients randomised to receive placebo during the DB treatment period were treated with G/P for 12 weeks (n=100)	Patients were randomised in a 2:1 ratio to: • G/P for 12 weeks (n=233) • SOF + DCV for 12 weeks (n=115) After enrolment in these two arms was complete, new patients were assigned to receive G/P for 8 weeks (n=157) Patients receiving SOF + DCV received one 400 mg tablet of SOF and one 60 mg tablet of DCV OD	G/P for 12 weeks (n=121)
Permitted and disallowed concomitant medication	Patients were on a stable dose of concomitant medications, which were confirmed to be safely administered with study drugs, for at least 2 weeks prior to initiation of study drugs. Patients were required to discontinue the prohibited medications and supplements listed below at least 2 weeks or 10 half-lives (whichever was longer) prior to the first dose of any study drug, and were not allowed to use these during the treatment period and for 30 days following discontinuation of study drugs • Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort • Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin • Atorvastatin, lovastatin, simvastatin			

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
	• Astemizole, cisapride, terfenadine • Ethinyl estradiol containing oral contraceptives and systemic immunosuppressants Patients were allowed to resume previously prohibited medications/supplements or revert to pre-study doses, 30 days following discontinuation of study drugs			
Primary outcomes (including scoring methods and timings of assessments)	SVR12 is defined as HCV RNA <LLOQ at 12 weeks after EOT • Non-inferiority of the percentage of patients achieving SVR12 in the 12-week arm ITT mono-infected GT1 DAA-naïve (ITT-PS) population compared to the historical efficacy established by current approved SoC regimens for this patient population (OBV/PTV/RTV + DSV ± RBV or SOF/LDV for 12 weeks) • Non-inferiority of the percentage of patients achieving SVR12 in the 8-week arm compared to the 12-week arm in the per protocol ITT mono-infected GT1 DAA-	• Non-inferiority of the percentage of patients in the ITT population receiving G/P during the DB treatment period, excluding patients who had previously failed treatment with SOF in combination with RBV ± peg-IFN, achieving SVR12 compared to the historical efficacy (SVR12 95%) of 12-week treatment with SOF + RBV • Safety	• Non-inferiority of the percentage of patients in the ITT population achieving SVR12 in the G/P 12-week arm compared to the SOF + DCV 12-week arm • Non-inferiority of the percentage of patients in the ITT population achieving SVR12 in the G/P 8-week arm compared to the G/P 12-week arm • Safety	• Percentage of patients in the ITT population achieving SVR12 • Safety

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
	naïve (ITT-PS-PP) population • Non-inferiority of the percentage of patients achieving SVR12 in the 8-week arm compared to the 12-week arm in ITT mono-infected GT1 DAA-naïve (ITT-PS) population			
Secondary outcomes (including scoring methods and timings of assessments)	• Percentage of patients achieving SVR12 at 12 weeks after EOT among: • The ITT mono-infected HCV GT1 population (ITT-MS) • The ITT population • Patients with HCV GT1/HIV-1 co-infection • Patients with prior SOF experience	• Superiority of the percentage of patients in ITT population receiving G/P during the DB treatment period, excluding patients who had previously failed treatment with SOF in combination with RBV ± peg-IFN, achieving SVR12 compared to the historical efficacy (SVR12 95%) of 12-week treatment with SOF + RBV • Percentage of patients in the ITT population who had previously failed treatment with	• Superiority of the percentage of patients in the ITT population achieving SVR12 in the G/P 12-week arm compared to the SOF + DCV 12-week arm	

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
		SOF, in combination with RBV ± peg-IFN achieving SVR12		
	• Percentage of patients in the ITT population (for ***ENDURANCE-2***, a modified ITT population was used that excluded patients who had previously failed treatment with SOF, in combination with RBV ± peg-IFN) with on-treatment virologic failure, defined as: • Confirmed >1 log10 IU/mL increase from nadir in HCV RNA at any time point during treatment, or • Confirmed HCV RNA ≥100 IU/mL after HCV RNA <LLOQ during treatment, or • HCV RNA ≥LLOQ at EOT with ≥6 weeks of treatment • Percentage of patients in the ITT population (for ***ENDURANCE-2***, a modified ITT population was used that excluded patients who had previously failed treatment with SOF, in combination with RBV ± peg-IFN) with post-treatment relapse, defined as confirmed HCV RNA ≥LLOQ between EOT and 12 weeks after EOT among patients who completed treatment with HCV RNA <LLOQ at EOT • For ***ENDURANCE-1***, on-treatment virologic failure and post-treatment relapse were also reported for the ITT-PS population			
Additional outcomes (including scoring methods and timings of assessments)	• The percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period (***ENDURANCE-2:*** in the double-blind treatment period) • The percentage of patients with SVR4 and SVR24 (sustained virologic response 4 and 24 weeks, respectively post-dosing) • The percentage of patients who relapsed after achieving SVR12 • ***ENDURANCE-4 only:*** The percentage of patients, excluding TE patients who failed a SOF-based regimen, achieving SVR12 • NGS to identify HCV variants at signature amino acid positions • Pharmacokinetics			

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
	• PROs using the EQ-5D-3L, and ***ENDURANCE-2, -3 and -4:*** SF-36v2, FSS, WPAI-HCV			
Pre-planned subgroups	When study arms were not divided by patient characteristics such as treatment or cirrhosis status, post-hoc analyses were performed to examine the results in these subgroups			

Abbreviations: DAA, direct-acting antiviral; DB, double-blind; DCV, daclatasvir; DSV, dasabuvir; EOT, end of treatment; EQ-5D-3L, EuroQol-5 Dimensions-three Level; FSS, Fatigue Severity Scale; G/P, glecaprevir/pibrentasvir; GLE, glecaprevir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IRT, interactive response technology; ITT, intention-to-treat; ITT-MS, ITT mono-infected HCV GT1 population; ITT-PS, ITT mono-infected GT1 DAA-naïve; ITT-PS-PP, per-protocol ITT-PS; IU, infectious unit; LLOQ, lower limit of quantitation; NC, non-cirrhotic; NGS, next generation sequencing; OBV, ombitasvir; OD, once-daily; OL, open-label; peg-IFN, pegylated IFN; PIB, pibrentasvir; PRO, patient reported outcome; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SF-36v2, SF-36 version 2; SoC, standard of care; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve; WPAI-HCV, Work Productivity Activity Impairment Hepatitis C Specific Instrument

B.2.3.6 EXPEDITION-1, SURVEYOR-I and SURVEYOR-II trials

Table 12: Comparative summary of methodology: EXPEDITION-1 and SURVEYOR-II, Parts 2 and 3

Trial number (acronym)	M14-172 (EXPEDITION-1)[56, 57]	M14-868 (SURVEYOR-II, Part 2)[58-64]	M14-868 (SURVEYOR-II, Part 3)[59, 63-65]
Clinicaltrials.gov identifier	NCT02642432	NCT02243293	
Study population	• GT1, GT2, GT4, GT5 or GT6 • TN or TE-PRS • CC • G/P treatment length: 12 weeks	• GT2, GT3 • TN or TE-PR • NC or CC (GT3 CC were TN only[a]; GT2 were NC only) • G/P treatment length: 8 or 12 weeks ± RBV	• GT3 • TN CC • TE-PRS NC CC • G/P treatment length: 12 or 16 weeks
Study objective	• To evaluate the efficacy of 12-week treatment with G/P in TN or TE-PRS CC patients as	• To evaluate the efficacy of 8- or 12-week treatment with G/P with or without RBV in TN or TE-PR NC and CC patients, as measured	• To evaluate the efficacy of 12- or 16-week treatment with G/P in GT3 TN CC patients and TE-PRS NC and CC patients, as measured

Trial number (acronym)	M14-172 (EXPEDITION-1)[56, 57]	M14-868 (SURVEYOR-II, Part 2)[58-64]	M14-868 (SURVEYOR-II, Part 3)[59, 63-65]
	measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of the treatment regimen	by the proportion of patients with SVR12 • To evaluate the safety and tolerability of each treatment regimen	by the proportion of patients with SVR12 • To evaluate the safety and tolerability of the treatment regimens
Location	40 study locations in the United States, Belgium, Canada, Germany, South Africa and Spain	For whole SURVEYOR-II study: 78 study locations in the United States, Australia, Canada, France, Korea, New Zealand and Taiwan, and 3 sites in the United Kingdom 4 patients in the United Kingdom were enrolled in Part 2	5 patients in the United Kingdom were enrolled in Part 3
Trial design	Multicentre, open-label, single-arm, Phase III	Multicentre, partially-randomised open-label, Phase II	
Method of randomisation	An IRT system was employed to manage drug dispensation and compliance, and (where applicable) patient randomisation and treatment assignment	Randomisation was stratified by presence or absence of cirrhosis and by prior HCV treatment history for CC patients	
Duration of study	Treatment duration: 12 weeks Follow-up: up to 24 weeks post-treatment	Treatment duration: 8 or 12 weeks depending on treatment assignment Follow-up: up to 24 weeks post-treatment	Treatment duration: 12 or 16 weeks depending on treatment assignment Follow-up: up to 24 weeks post-treatment
Settings and locations where data were collected	Data were collected at the trial sites listed above		
	Patients receiving G/P received three fixed-dose combination tablets containing 100 mg of GLE and 40 mg of PIB OD unless otherwise stated		

Trial number (acronym)	M14-172 (EXPEDITION-1)[56, 57]	M14-868 (SURVEYOR-II, Part 2)[58-64]	M14-868 (SURVEYOR-II, Part 3)[59, 63-65]
Intervention(s) (n=) and comparators(s) (n=)	G/P for 12 weeks (n=146)	In this trial patients receiving G/P received three 100 mg tablets of GLE and three 40 mg tablets of PIB OD GT2 NC patients were enrolled to receive G/P for 8 weeks (n=54) GT3 NC patients were enrolled to receive G/P for 8 (TN) or 12 (TE-PR) weeks (n=53) GT3 TN CC patients were randomised in a 1:1 ratio to: • G/P for 12 weeks (n=28)[a] • G/P + RBV for 12 weeks (n=27)[a] Patients receiving RBV received 800 mg OD	TE-PRS patients without cirrhosis were randomised at a 1:1 ratio to: • G/P for 12 weeks (n=22) • G/P for 16 weeks (n=22) TN patients with cirrhosis were only enrolled to receive G/P for 12 weeks (n=40) TE-PRS patients with cirrhosis were only enrolled to receive G/P for 16 weeks (n=47)
Permitted and disallowed concomitant medication	Patients were on a stable dose of concomitant medications, which were confirmed to be safely administered with study drugs, for at least 2 weeks prior to initiation of study drugs. Patients were required to discontinue the prohibited medications and supplements listed below at least 2 weeks or 10 half-lives (whichever was longer) prior to the first dose of any study drug, and were not allowed to use these during the treatment period and for 30 days following discontinuation of study drugs • Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort • Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin • Atorvastatin, lovastatin, simvastatin • Astemizole, cisapride, terfenadine • Ethinyl estradiol containing oral contraceptives and systemic immunosuppressants		

Trial number (acronym)	M14-172 (EXPEDITION-1)[56, 57]	M14-868 (SURVEYOR-II, Part 2)[58-64]	M14-868 (SURVEYOR-II, Part 3)[59, 63-65]
	• Patients were allowed to resume previously prohibited medications/supplements or revert to pre-study doses, 30 days following discontinuation of study drugs		
Primary outcomes (including scoring methods and timings of assessments)	• Percentage of patients in the ITT population achieving SVR12, as defined as HCV RNA <LLOQ at 12 weeks after EOT • Safety		
Secondary outcomes (including scoring methods and timings of assessments)	• ***SURVEYOR-II, Parts 2 and 3 only*****:** Percentage of patients achieving SVR4 (SVR4 is defined as HCV RNA <LLOQ at 4 weeks after EOT) • Percentage of patients with on-treatment virologic failure, defined as: • Confirmed >1 log10 IU/mL increase from nadir in HCV RNA at any time point during treatment, or • Confirmed HCV RNA ≥100 IU/mL after HCV RNA <LLOQ during treatment, or • HCV RNA ≥LLOQ at EOT with ≥6 weeks of treatment • Percentage of patients with post-treatment relapse, defined as confirmed HCV RNA ≥LLOQ between EOT and 12 weeks after EOT among patients who completed treatment with HCV RNA <LLOQ at EOT, ***SURVEYOR-II, Parts 2 and 3 only:*** excluding reinfection		
Additional outcomes (including scoring methods and timings of assessments)	• The percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • ***EXPEDITION-1 only*****:** The percentage of patients with SVR4 (sustained virologic response 4 weeks post-dosing) • The percentage of patients with SVR24 (sustained virologic response 24 weeks post-dosing) • The percentage of patients who relapsed after achieving SVR12 • NGS to identify HCV variants at signature amino acid positions • Pharmacokinetics		

Trial number (acronym)	M14-172 (EXPEDITION-1)[56, 57]	M14-868 (SURVEYOR-II, Part 2)[58-64]	M14-868 (SURVEYOR-II, Part 3)[59, 63-65]
	• PROs using the EQ-5D-3L (***EXPEDITION-1***) or EQ-5D-5L (***SURVEYOR-II, Parts 2 and 3***), SF-36v2, FSS, WPAI-HCV, and ***SURVEYOR-II, Parts 2 and 3 only***: HCVTSat		
Pre-planned subgroups	When study arms were not divided by patient characteristics such as treatment or cirrhosis status, post-hoc analyses were performed to examine the results in these subgroups		

[a]When SURVEYOR-II, Part 2 enrolment was initiated, both TN and TE-PR CC GT3-infected patients were eligible for enrolment. Enrolment was halted for TE-PR GT3-infected CC patients based on feedback from the United States Food and Drug Administration. As a result, 4 TE-PR patients randomised to receive G/P for 12 weeks had their treatment duration extended to 16 weeks. Three patients randomised to receive G/P + RBV for 12 weeks continued on the same treatment course.

Abbreviations: CC, compensated cirrhosis; EOT, end of treatment; EQ-5D-3L, EuroQol-5 Dimensions-three Level; EQ-5D-5L, EuroQol-5 Dimensions-five Level; FSS, Fatigue Severity Scale; G/P, glecaprevir/pibrentasvir; GLE, glecaprevir; GT, genotype; HCV, hepatitis C virus; HCVTSat, chronic HCV treatment satisfaction instrument; IFN, interferon; IRT, interactive response technology; ITT, intention-to-treat; IU, infectious unit; LLOQ, lower limit of quantitation; NC, non-cirrhotic; NGS, next generation sequencing; OD, once-daily; peg-IFN, pegylated IFN; PIB, pibrentasvir; PRO, patient reported outcome; RBV, ribavirin; RNA, ribonucleic acid; SF-36v2, SF-36 version 2; SOF, sofosbuvir; SVR, sustained virologic response; TE-PR, treatment-experienced with regimens containing peg-IFN/RBV; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve; WPAI-HCV, Work Productivity Activity Impairment Hepatitis C Specific Instrument

Table 13: Comparative summary of methodology: SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 trials

Trial number (acronym)	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66-68]	M14-868 (SURVEYOR-II, Part 1)[59, 60, 63, 64, 69]	M14-868 (SURVEYOR-II, Part 4)[59, 63, 64, 70]
Clinicaltrials.gov identifier	NCT02243280	NCT02243293	
Study population	• GT1, GT4, GT5 or GT6 • TN or TE-PR • GT1 NC and CC; GT4, GT5 and GT6 NC only • G/P treatment length: 8 or 12 weeks	• GT2, GT3 • TN or TE-PR) • NC • G/P treatment length: 12 weeks ± RBV	• GT2, GT4, GT5 or GT6 • TN or TE-PRS • NC • G/P treatment length: 8 weeks

Trial number (acronym)	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66-68]	M14-868 (SURVEYOR-II, Part 1)[59, 60, 63, 64, 69]	M14-868 (SURVEYOR-II, Part 4)[59, 63, 64, 70]
Study objective	• To evaluate the efficacy of 8-week or 12-week treatment with G/P in TN or TE-PR patients with (GT1 only) or without cirrhosis, as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of the treatment regimen	• To evaluate the efficacy of 12-week treatment with G/P with or without RBV in TN or TE-PR patients without cirrhosis, as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of the treatment regimen	• To compare the efficacy of 8-week treatment with G/P versus the historical efficacy of 12-week treatment with SOF + RBV, in GT2 DAA-TN patients without cirrhosis as measured by the proportion of patients with SVR12 • To evaluate the efficacy of 8 weeks of treatment with G/P in GT2, GT4, GT5 and GT6 TN and TE-PRS patients without cirrhosis, as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of the treatment regimens
Location	For whole SURVEYOR-I study, including Part 1: 28 study locations in the United States, New Zealand, Canada and Australia	For whole SURVEYOR-II study, including Parts 1 and 4: 78 study locations in the United States, Australia, Canada, France, Korea, New Zealand and Taiwan, and 3 sites in the United Kingdom No patients in the United Kingdom were enrolled in Part 1	No patients in the United Kingdom were enrolled in Part 4
Trial design	Multicentre, open-label, Phase II	Multicentre, randomised, open-label, Phase II	Multicentre, open-label, single-arm, Phase II
Method of randomisation	An IRT system was employed to manage drug dispensation and compliance, and (where applicable) patient randomisation and treatment assignment		
Duration of study	Treatment duration: 8 or 12 weeks	Treatment duration: 12 weeks	Treatment duration: 8 weeks

Trial number (acronym)	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66-68]	M14-868 (SURVEYOR-II, Part 1)[59, 60, 63, 64, 69]	M14-868 (SURVEYOR-II, Part 4)[59, 63, 64, 70]
	Follow-up: up to 24 weeks post-treatment	Follow-up: up to 24 weeks post-treatment	Follow-up: up to 24 weeks post-treatment
Settings and locations where data were collected	Data were collected at the trial sites listed above		
Intervention(s) (n=) and comparators(s) (n=)	Patients receiving G/P received three 100 mg tablets of GLE and three 40 mg tablets of PIB OD unless otherwise stated Patients were enrolled as follows: • GT1 NC patients: G/P (300 mg/120 mg) for 8 weeks (n=34) • GT1 CC patients: G/P (200 mg/120 mg) for 12 weeks (n=27) • GT4, GT5, and GT6 NC patients: G/P (300 mg/120 mg) for 12 weeks (n=34)	GT2 NC patients were randomised in a 1:1:1 ratio to: • G/P (300 mg/120 mg) for 12 weeks (n=25) • G/P (200 mg/120 mg) for 12 weeks (n=24) • G/P (200 mg/120 mg) + RBV for 12 weeks (n=25) Patients receiving RBV received 1,000 mg or 1,200 mg (weight based) divided twice daily GT3 NC patients were randomised in a 1:1:1:1 ratio to: • G/P (300 mg/120 mg) for 12 weeks (n=30) • G/P (200 mg/120 mg) for 12 weeks (n=31) • G/P (200 mg/120 mg) + RBV for 12 weeks (n=31) • G/P (200 mg/40 mg) for 12 weeks (n=30)	Patients in this study received three fixed-dose combination tablets containing 100 mg of GLE and 40 mg of PIB OD G/P for 8 weeks • GT2 (n=145) • GT4, GT5 or GT6 (n=58)

Trial number (acronym)	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66-68]	M14-868 (SURVEYOR-II, Part 1)[59, 60, 63, 64, 69]	M14-868 (SURVEYOR-II, Part 4)[59, 63, 64, 70]
Permitted and disallowed concomitant medication	Patients were on a stable dose of concomitant medications, which were confirmed to be safely administered with study drugs, for at least 2 weeks prior to initiation of study drugs. Patients were required to discontinue the prohibited medications and supplements listed below at least 2 weeks or 10 half-lives (whichever was longer) prior to the first dose of any study drug, and were not allowed to use these during the treatment period and for 30 days following discontinuation of study drugs • Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort • Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin • Atorvastatin, lovastatin, simvastatin • Astemizole, cisapride, terfenadine • Ethinyl estradiol containing oral contraceptives and systemic immunosuppressants Patients were allowed to resume previously prohibited medications/supplements or revert to pre-study doses, 30 days following discontinuation of study drugs		
Primary outcomes (including scoring methods and timings of assessments)	• Percentage of patients in the ITT population achieving SVR12. SVR12 is defined as HCV RNA <LLOQ at 12 weeks after EOT • ***SURVEYOR-II, Part 4 only:*** Non-inferiority of the percentage of GT2 DAA-TN NC patients in the ITT population achieving SVR12 compared to the historical efficacy (SVR12 95%) of 12-week treatment with SOF + RBV • Safety		
Secondary outcomes (including scoring methods and timings of assessments)	• Percentage of patients achieving SVR4 (SVR4 is defined as HCV RNA <LLOQ at 4 weeks after EOT) • Percentage of patients with on-treatment virologic failure, defined as: • Confirmed >1 log10 IU/mL increase from nadir in HCV RNA at any time point during treatment, or • Confirmed HCV RNA ≥LLOQ after HCV RNA <LLOQ during treatment, or • HCV RNA ≥100 IU/mL (***SURVEYOR-I, Part 2***: >LLOQ) at EOT with ≥6 weeks of treatment		

Trial number (acronym)	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66-68]	M14-868 (SURVEYOR-II, Part 1)[59, 60, 63, 64, 69]	M14-868 (SURVEYOR-II, Part 4)[59, 63, 64, 70]
	• Percentage of patients with post-treatment relapse, defined as confirmed HCV RNA ≥LLOQ between EOT and 12 weeks after EOT among patients who completed treatment with HCV RNA <LLOQ at EOT ***SURVEYOR-II, Parts 1 and 4 only:*** excluding reinfection		
Additional outcomes (including scoring methods and timings of assessments)	• The percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • The percentage of patients with SVR24 (sustained virologic response 24 weeks post-dosing) • The percentage of patients who relapsed after achieving SVR12 • NGS to identify HCV variants at signature amino acid positions • Pharmacokinetics • PROs using the EQ-5D-5L, HCVTSat, SF-36v2, FSS, WPAI-HCV		
Pre-planned subgroups	When study arms were not divided by patient characteristics such as treatment or cirrhosis status, post-hoc analyses were performed to examine the results in these subgroups		

Abbreviations: CC, compensated cirrhosis; DAA, direct-acting antiviral; EOT, end of treatment; EQ-5D-5L, EuroQol-5 Dimensions-five Level; FSS, Fatigue Severity Scale; G/P, glecaprevir/pibrentasvir; GLE, glecaprevir; GT, genotype; HCV, hepatitis C virus; HCVTSat, chronic HCV treatment satisfaction instrument; IFN, interferon; IRT, interactive response technology; ITT, intention-to-treat; IU, infectious unit; LLOQ, lower limit of quantitation; NC, non-cirrhotic; NGS, next generation sequencing; OD, once-daily; peg-IFN, pegylated IFN; PIB, pibrentasvir; PRO, patient reported outcome; RBV, ribavirin; RNA, ribonucleic acid; SF-36v2, SF-36 version 2; SOF, sofosbuvir; SVR, sustained virologic response; TE-PR, treatment-experienced with regimens containing peg-IFN/RBV; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve; WPAI-HCV, Work Productivity Activity Impairment Hepatitis C Specific Instrument

B.2.3.7 [redacted]EXPEDITION-4 and MAGELLAN-I trials

Table 14: Comparative summary of methodology: EXPEDITION-4 and MAGELLAN-1 trials

Trial number (acronym)	M15-462 (EXPEDITION-4)[38, 71, 72]	M15-410 (MAGELLAN-I, Part 1) [5, 39, 73, 74]	M15-410 (MAGELLAN-I, Part 2) [5, 40, 41, 73, 74]
Clinicaltrials.gov identifier	NCT02651194	NCT02446717	
Study population	• GT1, GT2, GT3, GT4, GT5 or GT6	• GT1	• GT1, GT4, GT5 or GT6

Trial number (acronym)	M15-462 (EXPEDITION-4)[38, 71, 72]	M15-410 (MAGELLAN-I, Part 1) [5, 39, 73, 74]	M15-410 (MAGELLAN-I, Part 2) [5, 40, 41, 73, 74]
	• TN (all genotypes) or TE-PRS (GT1, GT2, GT4, GT5 or GT6) • NC or CC • Who had severe renal impairment or end-stage renal disease (including those on dialysis) • G/P treatment length: 12 weeks	• TE-DAA • NC Note that this patient population is not within the anticipated licence for G/P • G/P treatment length: 12 weeks ± RBV	• TE-DAA • NC or CC Note that this patient population is not within the anticipated licence for G/P • G/P treatment length: 12 or 16 weeks
Study objective	• To evaluate the efficacy of 12-week treatment with G/P in TN or TE-PRS NC and CC patients with or without stage 4 or 5 CKD, as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of the treatment regimen	• To evaluate the efficacy of 12-week treatment with G/P with or without RBV in patients without cirrhosis who had failed a prior anti-HCV DAA-containing regimen, as measured by the proportion of patients with SVR12 • To evaluate the pharmacokinetics of G/P and RBV, and to evaluate the role of RBV	• To evaluate the efficacy of 12-week or 16-week treatment with G/P in NC and CC patients who had failed a prior anti-HCV DAA-containing regimen, as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of the treatment regimen
Location	28 study locations in the United States, Australia, Belgium, Canada, France, Greece, Italy and New Zealand, and 2 sites (7 patients) in the United Kingdom	For whole MAGELLAN-1 study: 30 study locations in the United States, Australia, France, and Spain, and 1 site in the United Kingdom. No patients in the United Kingdom were enrolled in Part 1	2 patients in the United Kingdom were enrolled in Part 2
Trial design	Multicentre, open-label, single-arm, Phase III	Multicentre, randomised, open-label, Phase II	
Method of randomisation	An IRT system was employed to manage drug dispensation and compliance, and (where applicable) patient randomisation and treatment assignment		
		Randomisation was stratified by: • GT1 subtype (1b or non-1b)	Randomisation was stratified by genotype and by previous experience to two DAA regimen classes

Trial number (acronym)	M15-462 (EXPEDITION-4)[38, 71, 72]	M15-410 (MAGELLAN-I, Part 1) [5, 39, 73, 74]	M15-410 (MAGELLAN-I, Part 2) [5, 40, 41, 73, 74]
		• Previous experience to any of the following DAA regimen classes: ○ NS5A inhibitor (±PI)-experienced (e.g. SOF + DCV, DCV + ASV, DCV + SMV, LDV + SOF, OBV + PTV/RTV, or ○ NS5A inhibitor-naïve/PI-experienced (e.g. SMV + SOF, SMV + peg-IFN + RBV, TVR + peg-IFN + RBV, BOC + peg-IFN + RBV) ○ All other previous DAA-containing regimens not captured above (e.g. SOF + peg-IFN + RBV, SOF + RBV)	• NS5A inhibitor (±PI)-experienced, limited to DCV-, LDV-, or OBV-containing combination regimens • NS5A inhibitor-naïve/NS3/4A PI-experienced, limited to: PTV/RTV, SMV-, TVR-, or BOC-containing combination regimens
Duration of study	Treatment duration: 12 weeks Follow-up: up to 24 weeks post-treatment	Treatment duration: 12 weeks Follow-up: up to 24 weeks post-treatment	Treatment duration: 12 or 16 weeks depending on treatment assignment Follow-up: up to 24 weeks post-treatment
Settings and locations where data were collected	Data were collected at the trial sites listed above		
Intervention(s) (n=) and comparators(s) (n=)	Patients receiving G/P received three fixed-dose combination tablets containing 100 mg of GLE and 40 mg of PIB OD unless otherwise stated G/P for 12 weeks (n=104)	In this study, patients received three 100 mg tablets of GLE and three 40 mg tablets of PIB OD unless otherwise stated Patients were randomised in a 1:1 to:	Patients were randomised in a 1:1 to: • G/P for 12 weeks (n=44) • G/P for 16 weeks (n=47)

Trial number (acronym)	M15-462 (EXPEDITION-4)[38, 71, 72]	M15-410 (MAGELLAN-I, Part 1) [5, 39, 73, 74]	M15-410 (MAGELLAN-I, Part 2) [5, 40, 41, 73, 74]
		• G/P + RBV for 12 weeks (n=22) • G/P for 12 weeks (n=22) Patients receiving RBV received 800 mg OD The original study protocol specified randomisation at a 1:1:1 ratio including an arm with G/P (200 mg/80 mg)for 12 weeks. Enrolment into this arm was stopped after 6 patients enrolled based upon the decision not to pursue the development of this dose, after which patients were randomised as above	
Permitted and disallowed concomitant medication	Patients were on a stable dose of concomitant medications, which were confirmed to be safely administered with study drugs, for at least 2 weeks prior to initiation of study drugs. Patients were required to discontinue the prohibited medications and supplements listed below at least 2 weeks or 10 half-lives (whichever was longer) prior to the first dose of any study drug, and were not allowed to use these during the treatment period and for 30 days following discontinuation of study drugs • Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort • Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin • Atorvastatin, lovastatin, simvastatin • Astemizole, cisapride, terfenadine • Ethinyl estradiol containing oral contraceptives and systemic immunosuppressants Patients were allowed to resume previously prohibited medications/supplements or revert to pre-study doses, 30 days following discontinuation of study drugs		
Primary outcomes (including scoring methods and timings of assessments)	• Percentage of patients in the ITT population achieving SVR12. SVR12 is defined as HCV RNA <LLOQ at 12 weeks after EOT • Safety		

Trial number (acronym)	M15-462 (EXPEDITION-4)[38, 71, 72]	M15-410 (MAGELLAN-I, Part 1) [5, 39, 73, 74]	M15-410 (MAGELLAN-I, Part 2) [5, 40, 41, 73, 74]

Secondary outcomes (including scoring methods and timings of assessments)	• ***MAGELLAN-I, Parts 1 and 2 only*:** Percentage of patients achieving SVR4 (SVR4 is defined as HCV RNA <LLOQ at 4 weeks after EOT)
	• Percentage of patients with on-treatment virologic failure, defined as:
	  ○ Confirmed >1 log10 IU/mL increase from nadir in HCV RNA at any time point during treatment or
	  ○ Confirmed HCV RNA ≥LLOQ after HCV RNA <LLOQ during treatment, or
	  ○ HCV RNA ≥LLOQ at EOT with ≥6 weeks of treatment
	• Percentage of patients with post-treatment relapse, defined as confirmed HCV RNA ≥LLOQ between EOT and 12 weeks after EOT among patients who completed treatment with HCV RNA <LLOQ at EOT		

Additional outcomes (including scoring methods and timings of assessments)	• The percentage of patients with HCV RNA <LLOQ at each post-baseline visit in the treatment period • ***EXPEDITION-4 only*:** The percentage of patients with SVR4 (sustained virologic response 4 weeks post-dosing) • The percentage of patients with SVR24 (sustained virologic response 24 weeks post-dosing) • The percentage of patients who relapsed after achieving SVR12 • NGS to identify HCV variants at signature amino acid positions • Pharmacokinetics • ***EXPEDITION-4 only:*** PROs using the EQ-5D-3L SF-36v2, FSS, and WPAI-HCV		
Pre-planned subgroups	When study arms were not divided by patient characteristics such as treatment or cirrhosis status, post-hoc analyses were performed to examine the results in these subgroups		

Abbreviations: ASV, asunaprevir; BOC, boceprevir; CC, compensated cirrhosis; CKD, chronic kidney disease; DAA, direct-acting antiviral; DCV, daclatasvir; EOT, end of treatment; EQ-5D-3L, EuroQol-5 Dimensions-three Level; FSS, Fatigue Severity Scale; G/P, glecaprevir/pibrentasvir; GLE, glecaprevir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; IRT, interactive response technology; ITT, intention-to-treat; IU, infectious unit; LLOQ, lower limit of quantitation; LDV, ledipasvir; NC, non-cirrhotic; NGS, next generation sequencing; OD, once-daily; peg-IFN, pegylated IFN; OBV, ombitasvir; PI, protease inhibitor; PIB, pibrentasvir; PRO, patient reported outcome; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SF-36v2, SF-36 version 2; SOF, sofosbuvir; SMV, simeprevir; SVR, sustained virologic response; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TE, treatment-experienced; TN, treatment-naïve; TVR, telaprevir; WPAI-HCV, Work Productivity Activity Impairment Hepatitis C Specific Instrument

B.2.3.8 Additional trials

No additional information is included here regarding EXPEDITION-2 and MAGELLAN-II, which have only recently been completed.

Two trials in Japanese patients with CHC have been conducted: CERTAIN-1 and CERTAIN-2. Their methodology is described briefly here, though it should be noted that the fact that these two trials were conducted entirely in Japanese patients considerably limits their generalisability to the UK setting. Therefore, given the considerable body of evidence available from trials in global populations, including European and UK patients, presentation of these two studies in Japanese patients is restricted in this submission to a brief description of methodology and primary efficacy results. These studies were also excluded from the economic analysis.

B.2.3.8.1 CERTAIN-1

The CERTAIN-1 trial (NCT02707952) is a Phase III, partially-randomised, open-label, multicentre study to evaluate the efficacy of G/P in Japanese adults with CHC, composed of two sub-studies.[75-77] The objectives of the study were to determine the safety and efficacy of G/P treatment in CHC.

Sub-study 1 is a randomised study in GT1-infected NC patients. Patients without Y93H polymorphisms were randomised at a 2:1 ratio to receive either 8 weeks of treatment with G/P (300 mg/120 mg) or 12 weeks of treatment with OBV/PTV/RTV. All patients with Y93H polymorphisms were enrolled to receive 8 weeks of treatment with G/P (300 mg/120 mg).

Sub-study 2 is a non-randomised study in GT1- or GT2-infected CC patients; GT3-, GT4-, GT5-, or GT6-infected NC and CC patients; GT1- or GT2-infected NC and CC patients who had failed prior DAA treatments; and GT1- or GT2-infected patients with severe renal impairment and CC. All patients were enrolled to receive G/P (300 mg/120 mg) for 12 weeks. Finally, GT1- or GT2-infected NC patients with severe renal impairment received G/P (300 mg/120 mg) for 8 weeks.

295 patients were enrolled. The primary efficacy endpoint tested the non-inferiority of the SVR12 rate in the 8-week G/P arm to the 12-week OBV/PTV/RTV arm in sub-study 1. The secondary efficacy endpoints were in line with the studies in the previous Section (SVR12 rate in each study arm, percentage of patients with on-treatment virologic failure and post-treatment relapse). Additional outcomes included safety, resistance, and patient reported outcomes (PROs).

B.2.3.8.2 CERTAIN-2

The CERTAIN-2 trial (NCT02723084) is a Phase III, randomised, open-label, multicentre study to evaluate the efficacy of G/P in Japanese NC adults with chronic GT2 HCV infection.[75, 78-80] The objectives of the study are to determine the safety and efficacy of G/P treatment.

GT2-infected NC DAA-TN patients were randomised at a 2:1 ratio to receive G/P (300 mg/120 mg) for 8 weeks or SOF + RBV for 12 weeks. 136 patients were enrolled. The primary efficacy endpoint tested the non-inferiority of the SVR12 rate in the 8-week G/P arm to the 12-week SOF + RBV arm. The secondary efficacy endpoints were in line with CERTAIN-1.

B.2.4 *Eligibility criteria*

The key differences across trials relate to HCV genotypes, presence or absence of CC, and treatment history. The key inclusion and exclusion criteria across these trials are summarised in Table 15.

Eligibility criteria for individual trials can be found in Appendix Section D.3.

Table 15: Key eligibility criteria for the relevant trials

Key inclusion criteria	Key exclusion criteria
• Male or female, at least 18 years of age at time of screening • Patient had positive anti-HCV antibody and plasma HCV RNA viral load ≥1,000 IU/mL at screening • Chronic HCV infection defined as 1 of the following: • Confirmed >1 log10 IU/mL increase from nadir in HCV RNA at any time point during treatment, or • Positive for anti-HCV antibody or HCV RNA at least 6 months before screening, or • A liver biopsy consistent with CHC; or • Abnormal alanine aminotransferase levels for at least 6 months before screening • BMI is ≥18 kg/m^2 at the time of screening • Voluntarily signed and dated an informed consent form, approved by an • Institutional Review Board/Independent Ethics Committee prior to the • Initiation of any screening or study specific procedures • Able to understand and adhere to the study visit schedule and all other protocol requirements	• History of severe, life-threatening or other significant sensitivity to excipients of the study drug • Positive test result at screening for hepatitis B surface antigen (all studies) or anti-HIV-1 antibody (except ENDURANCE-1) • Females who are pregnant or intending to become pregnant, or breastfeeding, and males with a female partner who was pregnant or is intending to become pregnant during the course of the study • HCV genotyping performed during screening indicating co-infection with more than 1 HCV genotype • Any cause of liver disease other than CHC • Consideration by the investigator, for any reason, that the patient was an unsuitable candidate to receive GLE, PIB, or G/P • Child-Pugh B or C or history of liver decompensation

Abbreviations: BMI, body mass index; CHC, chronic HCV infection; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GLE, glecaprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IU, infectious unit; PIB, pibrentasvir

B.2.4.1 Overview of baseline characteristics and demographics for the relevant randomised controlled trials

Please refer to Table 10 in Section B.2.3.1 for an overview of the trials providing evidence in each of the different patient populations based on genotype, cirrhosis status and treatment

history. An overview of baseline characteristics and demographics for the relevant trials is provided below. Baseline characteristics and demographics are described in detail for each trial in Section B.2.4.2.

- In the ENDURANCE trials, which only enrolled NC patients, within each study the different groups had balanced characteristics. In ENDURANCE-1, -2 and -4, the majority of patients were TN; ENDURANCE-3 only enrolled TN patients.
- The patients in SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 were balanced in characteristics between groups and with a majority of TN patients.
- In the EXPEDITION-1 trial, the majority of patients were TN. A baseline Child-Pugh score of 5 was most common.
- The patients in SURVEYOR-II, Parts 2 and 3 were balanced in characteristics between groups and with a majority of TN patients in Part 2. Of the CC patients in Parts 2 and 3, the majority had a Child-Pugh score of 5.
- In the EXPEDITION-2 trial, the majority of patients were TN and NC.
- In the EXPEDITION-4 trial, the majority of patients were TN and with a baseline Child-Pugh score of 5.
- In the MAGELLAN-1 trial, the patients were balanced in characteristics between groups. There were an equal number of PI-experienced/NS5A-naïve patients and NS5A-experienced patients, except in Part 2, in which there were more NS5A-experienced patients. In Part 2, the majority of patients were NC. Of the CC patients in Part 2, the majority had a Child-Pugh score of 5.
- In the MAGELLAN-II trial, the majority of patients were TN and had received a liver (as opposed to a renal) transplant.

.

B.2.4.2 Baseline characteristics and demographics for the relevant randomised controlled trials

B.2.4.2.1 ENDURANCE trials

Baseline characteristics are summarised in Table 16 and genotype distribution in Table 17.

Table 16: Characteristics of participants in the ENDURANCE trials

Trial	M13-590 (ENDURANCE-1)[44, 46] (n=703)		M15-464 (ENDURANCE-2)[47, 49] (n=302)		M13-594 (ENDURANCE-3)[50, 52] (n=505)			M13-583 (ENDURANCE-4)[53, 55] (n=121)
Baseline characteristic, n (%)	**G/P 12 weeks (n=352)**	**G/P 8 weeks (n=351)**	**G/P 12 weeks (n=202)**	**Placebo 12 weeks (n=100)**	**G/P 12 weeks (n=233)**	**SOF + DCV 12 weeks (n=115)**	**G/P 8 weeks (n=157)**	**G/P 12 weeks (n=121)**
Age (years)								
Category 1: <65	317 (90.1)	309 (88.0)	136 (67.3)	66 (66.0)	[redacted]	[redacted]	[redacted]	108 (89.3)
Category 1: ≥65	35 (9.9)	42 (12.0)	66 (32.7)	34 (34.0)	[redacted]	[redacted]	[redacted]	13 (10.7)
Category 2: <75	349 (99.1)	346 (98.6)	191 (94.6)	95 (95.0)	[redacted]	[redacted]	[redacted]	118 (97.5)
Category 2: ≥75	3 (0.9)	5 (1.4)	11 (5.4)	5 (5.0)	[redacted]	[redacted]	[redacted]	3 (2.5)
BMI (kg/m^2) <30	299 (84.9)	300 (85.5)	170 (84.2)	82 (82.0)	[redacted]	[redacted]	[redacted]	100 (82.6)
BMI (kg/m^2) ≥30	53 (15.1)	51 (14.5)	32 (15.8)	18 (18.0)	[redacted]	[redacted]	[redacted]	21 (17.4)
Male	176 (50.0)	167 (47.6)	98 (48.5)	45 (45.0)	121 (51.9)	52 (45.2)	92 (58.6)	77 (63.6)
Race								
White	302 (85.8)	289 (82.3)	121 (59.9)	60 (60.0)	205 (88.0)	103 (89.6)	134 (85.4)	84 (71.2)
Black or African American	12 (3.4)	14 (4.0)	7 (3.5)	7 (7.0)	[redacted]	[redacted]	[redacted]	8 (6.8)
Asian	34 (9.7)	44 (12.5)	69 (34.2)	32 (32.0)	[redacted]	[redacted]	[redacted]	24 (20.3)
Other	4 (1.1)	4 (1.2)	5 (2.5)	1 (1.0)	[redacted]	[redacted]	[redacted]	2 (1.7)
Missing	-	-	-	-	-	-	-	3
Baseline fibrosis stage								

Trial	M13-590 (ENDURANCE-1)[44, 46] (n=703)		M15-464 (ENDURANCE-2)[47, 49] (n=302)		M13-594 (ENDURANCE-3)[50, 52] (n=505)			M13-583 (ENDURANCE-4)[53, 55] (n=121)
Baseline characteristic, n (%)	**G/P 12 weeks (n=352)**	**G/P 8 weeks (n=351)**	**G/P 12 weeks (n=202)**	**Placebo 12 weeks (n=100)**	**G/P 12 weeks (n=233)**	**SOF + DCV 12 weeks (n=115)**	**G/P 8 weeks (n=157)**	**G/P 12 weeks (n=121)**
F0–F1	298 (84.9)	296 (85.1)	154 (76.2)	85 (85.0)	201 (86.3)	97 (84.3)	122 (77.7)	104 (86.0)
F2	24 (6.8)	22 (6.3)	18 (8.9)	9 (9.0)	12 (5.2)	8 (7.0)	8 (5.1)	8 (6.6)
F3	29 (8.3)	30 (8.6)	30 (14.9)	6 (6.0)	20 (8.6)	10 (8.7)	27 (17.2)	9 (7.4)
F4	0	0	-	-	0	0	0	0
Missing	1	3	-	-	-	-	-	-
Prior HCV treatment history								
Naïve	217 (61.6)	219 (62.4)	141 (69.8)	71 (71.0)	233 (100)	115 (100)	157 (100)	82 (67.8)
Experienced	135 (38.4)	132 (37.6)	61 (30.2)	29 (29.0)	N/A	N/A	N/A	39 (32.2)
Type of previous regimen								
IFN-based	133 (38.4)	131 (37.3)	55 (27.2)	27 (27.0)	N/A	N/A	N/A	39 (32.2)
SOF-based	2 (0.6)	1 (0.3)	6 (3.0)	2 (2.0)	N/A	N/A	N/A	0
Type of response to previous treatment								
Breakthrough/ on-treatment non-responder	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]
Post-treatment relapse	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]
Unknown/other	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]
IL28B genotype								
CC	86 (24.4)	102 (29.1)	91 (45.0)	50 (50.0)	[redacted]	[redacted]	[redacted]	30 (24.8)
CT	210 (59.7)	197 (56.1)	73 (36.1)	37 (37.0)	[redacted]	[redacted]	[redacted]	68 (56.2)
TT	56 (15.9)	52 (14.8)	38 (18.8)	13 (13.0)	[redacted]	[redacted]	[redacted]	23 (19.0)
Baseline HCV RNA level (IU/mL)								

Trial	M13-590 (ENDURANCE-1)[44, 46] (n=703)		M15-464 (ENDURANCE-2)[47, 49] (n=302)		M13-594 (ENDURANCE-3)[50, 52] (n=505)			M13-583 (ENDURANCE-4)[53, 55] (n=121)
Baseline characteristic, n (%)	**G/P 12 weeks (n=352)**	**G/P 8 weeks (n=351)**	**G/P 12 weeks (n=202)**	**Placebo 12 weeks (n=100)**	**G/P 12 weeks (n=233)**	**SOF + DCV 12 weeks (n=115)**	**G/P 8 weeks (n=157)**	**G/P 12 weeks (n=121)**
Category 1: <6,000,000	309 (87.8)	302 (86.0)	155 (76.7)	82 (82.0)	[redacted]	[redacted]	[redacted]	99 (81.8)
Category 1: ≥6,000,000	43 (12.2)	49 (14.0)	47 (23.3)	18 (18.0)	[redacted]	[redacted]	[redacted]	22 (18.2)
Category 2: <10,000,000	336 (95.5)	335 (95.4)	183 (90.6)	93 (93.0)	[redacted]	[redacted]	[redacted]	116 (95.9)
Category 2: ≥10,000,000	16 (4.5)	16 (4.6)	19 (9.4)	7 (7.0)	[redacted]	[redacted]	[redacted]	5 (4.1)
Other characteristics								
HCV mono-infected	334 (94.9)	336 (95.7)	202 (100)	100 (100)	233 (100)	115 (100)	157 (100)	121 (100)
HCV/HIV-1 co infected	18 (5.1)	15 (4.3)	-	-	-	-	-	-

Abbreviations: BMI, body mass index; DCV, daclatasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IL28B, interleukin-28b; RNA, ribonucleic acid; SOF, sofosbuvir

Table 17: HCV genotypes and subtypes of participants in the ENDURANCE trials

Trial	M13-590 (ENDURANCE-1)[44, 46] (n=703)		M15-464 (ENDURANCE-2)[47, 49] (n=302)		M13-594 (ENDURANCE-3) [50, 52] (n=505)			M13-583 (ENDURANCE-4)[53, 55] (n=121)
GT, n (%)	**G/P 12 weeks (n=352)**	**G/P 8 weeks (n= 351)**	**G/P 12 weeks (n=202)**	**Placebo 12 weeks (n=100)**	**G/P 12 weeks (n=233)**	**SOF + DCV 12 weeks (n=115)**	**G/P 8 weeks (n=157)**	**G/P 12 weeks (n=121)**
1 (total)	[redacted]	[redacted]	-	-	-	-	-	-
1[a]	[redacted]	[redacted]	-	-	-	-	-	-

Trial	M13-590 (ENDURANCE-1)[44, 46] (n=703)		M15-464 (ENDURANCE-2)[47, 49] (n=302)		M13-594 (ENDURANCE-3) [50, 52] (n=505)			M13-583 (ENDURANCE-4)[53, 55] (n=121)
GT, n (%)	G/P 12 weeks (n=352)	G/P 8 weeks (n= 351)	G/P 12 weeks (n=202)	Placebo 12 weeks (n=100)	G/P 12 weeks (n=233)	SOF + DCV 12 weeks (n=115)	G/P 8 weeks (n=157)	G/P 12 weeks (n=121)
1a	148 (42.0)	152 (43.3)	-	-	-	-	-	-
1b	[redacted]	[redacted]	-	-	-	-	-	-
1g	[redacted]	[redacted]	-	-	-	-	-	-
2 (total)	-	-	202 (100)	100 (100)	-	-	-	-
2[a]	-	-	79 (39.1)	39 (39.0)	-	-	-	-
2a/2c	-	-	76 (37.6)	40 (40.0)	-	-	-	-
2b	-	-	46 (22.8)	21 (21.0)	-	-	-	-
2i	-	-	1 (0.5)	0	-	-	-	-
3 (total)	-	-	-	-	233 (100)	115 (100)	157 (100)	
3[a]	-	-	-	-	[redacted]	[redacted]	[redacted]	-
3a	-	-	-	-	[redacted]	[redacted]	[redacted]	-
3b	-	-	-	-	[redacted]	[redacted]	[redacted]	-
4 (total)	-	-			-	-	-	76 (62.8)
4[a]	-	-	-	-	-	-	-	[redacted]
4a	-	-	-	-	-	-	-	[redacted]
4a/4c/4d	-	-	-	-	-	-	-	[redacted]
4e	-	-	-	-	-	-	-	[redacted]
4f	-	-	-	-	-	-	-	[redacted]
4h	-	-	-	-	-	-	-	[redacted]
4r	-	-	-	-	-	-	-	[redacted]
5 (total)	-	-	-	-	-	-	-	26 (21.5)
5a	-	-	-	-	-	-	-	26 (21.5)
6 (total)	-	-	-	-	-	-	-	19 (15.7)

Trial	M13-590 (ENDURANCE-1)[44, 46] (n=703)		M15-464 (ENDURANCE-2)[47, 49] (n=302)		M13-594 (ENDURANCE-3) [50, 52] (n=505)			M13-583 (ENDURANCE-4)[53, 55] (n=121)
GT, n (%)	G/P 12 weeks (n=352)	G/P 8 weeks (n= 351)	G/P 12 weeks (n=202)	Placebo 12 weeks (n=100)	G/P 12 weeks (n=233)	SOF + DCV 12 weeks (n=115)	G/P 8 weeks (n=157)	G/P 12 weeks (n=121)
6[a]	-	-	-	-	-	-	-	[redacted]
6a/6b	-	-	-	-	-	-	-	[redacted]
6c-1	-	-	-	-	-	-	-	[redacted]
6h	-	-	-	-	-	-	-	[redacted]

[a]Subtype could not be determined
Abbreviations: DCV, daclatasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; SOF, sofosbuvir

B.2.4.2.2 SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 trials

Baseline characteristics are summarised in Table 18 and genotype distribution in Table 19.

Table 18: Characteristics of participants in the SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 trials

Trial	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66, 68] (n=95)			M14-868 (SURVEYOR-II, Part 1)[59, 60, 64, 69] (n=195)							M14-868 (SURVEYOR-II, Part 4)[59, 64, 65] (n=203)	
Baseline characteristic, n (%)	GT1 NC G/P (300 mg/120 mg) 8 weeks (n=34)	GT1 CC G/P (200 mg/120 mg) 12 weeks (n=27)	GT4, GT5, GT6 NC G/P (300 mg/120 mg) 12 weeks (n=32)[a]	GT2 G/P (300 mg/120 mg) 12 weeks (n=25)	GT2 G/P (200 mg/120 mg) 12 weeks (n=24)	GT2 G/P (200 mg/120 mg) + RBV 12 weeks (n=25)	GT3 G/P (300 mg/120 mg) 12 weeks (n=30)	GT3 G/P (200 mg/120 mg) 12 weeks (n=30)	GT3 G/P (200 mg/120 mg) + RBV 12 weeks (n=31)	GT3 G/P (200 mg/40 mg) 12 weeks (n=30)	GT2 G/P 8 weeks (n=145)	GT4, GT5, or GT6 G/P 8 weeks (n=58)
Age (years)												
Category 1: <65	28 (82.4)	23 (85.2)	26 (81.3)	21 (84.0)	21 (87.5)	22 (88.0)	28 (93.3)	29 (96.7)	30 (96.8)	28 (93.3)	128 (88.3)	49 (84.5)

Trial	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66, 68] (n=95)			M14-868 (SURVEYOR-II, Part 1)[59, 60, 64, 69] (n=195)							M14-868 (SURVEYOR-II, Part 4)[59, 64, 65] (n=203)	
Baseline characteristic, n (%)	**GT1 NC G/P (300 mg/120 mg) 8 weeks (n=34)**	**GT1 CC G/P (200 mg/120 mg) 12 weeks (n=27)**	**GT4, GT5, GT6 NC G/P (300 mg/120 mg) 12 weeks (n=32)[a]**	**GT2 G/P (300 mg/120 mg) 12 weeks (n=25)**	**GT2 G/P (200 mg/120 mg) 12 weeks (n=24)**	**GT2 G/P (200 mg/120 mg) + RBV 12 weeks (n=25)**	**GT3 G/P (300 mg/120 mg) 12 weeks (n=30)**	**GT3 G/P (200 mg/120 mg) 12 weeks (n=30)**	**GT3 G/P (200 mg/120 mg) + RBV 12 weeks (n=31)**	**GT3 G/P (200 mg/40 mg) 12 weeks (n=30)**	**GT2 G/P 8 weeks (n=145)**	**GT4, GT5, or GT6 G/P 8 weeks (n=58)**
Category 1: ≥65	6 (17.6)	4 (14.8)	6 (18.8)	4 (16.0)	3 (12.5)	3 (12.0)	2 (6.7)	1 (3.3)	1 (3.2)	2 (6.7)	17 (11.7)	9 (15.5)
BMI (kg/m^2) <30	24 (70.6)	18 (66.7)	27 (84.4)	15 (60.0)	20 (83.3)	20 (80.0)	24 (80.0)	20 (66.7)	26 (83.9)	24 (80.0)	100 (69.0)	50 (86.2)
BMI (kg/m^2) ≥30	10 (29.4)	9 (33.3)	5 (15.6)	10 (40.0)	4 (16.7)	5 (20.0)	6 (20.0)	10 (33.3)	5 (16.1)	6 (20.0)	45 (31.0)	8 (13.8)
Male	19 (55.9)	20 (74.1)	16 (50.0)	16 (64.0)	13 (54.2)	18 (72.0)	19 (63.3)	14 (46.7)	19 (61.3)	15 (50.0)	61 (42.1)	37 (63.8)
Race												
White	33 (97.1)	24 (88.9)	18 (56.3)	22 (88.0)	22 (91.7)	23 (92.0)	29 (96.7)	27 (90.0)	29 (93.5)	28 (93.3)	120 (82.8)	35 (60.3)
Black or African American	1 (2.9)	2 (7.4)	4 (12.5)	2 (8.0)	1 (4.2)	2 (8.0)	1 (3.3)	1 (3.3)	1 (3.2)	1 (3.3)	11 (7.6)	10 (17.2)
Asian	0	0	9 (28.1)	1 (4.0)	1 (4.2)	0	0	0	1 (3.2)	0	10 (6.9)	13 (22.4)
Other	0	1 (3.7)	1 (3.1)	0	0	0	0	2 (6.7)	0	1 (3.3)	4 (2.8)	0
Baseline fibrosis stage												
F0–F1	24 (70.6)	0	24 (75.0)	16 (64.0)	18 (75.0)	18 (72.0)	18 (60.0)	16 (53.3)	18 (58.1)	19 (63.3)	123 (84.8)	47 (81.0)

Trial	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66, 68] (n=95)			M14-868 (SURVEYOR-II, Part 1)[59, 60, 64, 69] (n=195)							M14-868 (SURVEYOR-II, Part 4)[59, 64, 65] (n=203)	
Baseline characteristic, n (%)	**GT1 NC G/P (300 mg/120 mg) 8 weeks (n=34)**	**GT1 CC G/P (200 mg/120 mg) 12 weeks (n=27)**	**GT4, GT5, GT6 NC G/P (300 mg/120 mg) 12 weeks (n=32)[a]**	**GT2 G/P (300 mg/120 mg) 12 weeks (n=25)**	**GT2 G/P (200 mg/120 mg) 12 weeks (n=24)**	**GT2 G/P (200 mg/120 mg) + RBV 12 weeks (n=25)**	**GT3 G/P (300 mg/120 mg) 12 weeks (n=30)**	**GT3 G/P (200 mg/120 mg) 12 weeks (n=30)**	**GT3 G/P (200 mg/120 mg) + RBV 12 weeks (n=31)**	**GT3 G/P (200 mg/40 mg) 12 weeks (n=30)**	**GT2 G/P 8 weeks (n=145)**	**GT4, GT5, or GT6 G/P 8 weeks (n=58)**
F2	6 (17.6)	0	4 (12.5)	6 (24.0)	4 (16.7)	3 (12.0)	6 (20.0)	10 (33.3)	6 (19.4)	7 (23.3)	9 (6.2)	3 (5.2)
F3	4 (11.8)	0	4 (12.5)	3 (12.0)	2 (8.3)	4 (16.0)	6 (20.0)	4 (13.3)	7 (22.6)	2 (6.7)	13 (9.0)	8 (13.8)
F4	0	26 (96.3)	0	0	0	0	0	0	0	2 (6.7)[b]	0	0
Missing	-	1 (3.7)	-	-	-	-	-	-	-	-	-	-
Prior HCV treatment history												
Naïve	29 (85.3)	21 (77.8)	27 (84.4)	22 (88.0)	22 (91.7)	22 (88.0)	27 (90.0)	27 (90.0)	28 (90.3)	28 (93.3)	127 (87.6)	49 (84.5)
Experienced	5 (14.7)	6 (22.2)	5 (15.6)	3 (12.0)	2 (8.3)	3 (12.0)	3 (10.0)	3 (10.0)	3 (9.7)	2 (6.7)	18 (12.4)	9 (15.5)
Type of previous regimen												
IFN-based	-	-	-	-	-	-	-	-	-	-	12 (8.3)	9 (15.5)
SOF-based	-	-	-	-	-	-	-	-	-	-	6 (4.1)	0
IL28B genotype												
CC	11 (32.4)	4 (14.8)	13 (40.6)	13 (52.0)	13 (54.2)	12 (48.0)	10 (33.3)	11 (36.7)	11 (35.5)	12 (40.0)	69 (47.6)	19 (32.8)
Non-CC	23 (67.6)	23 (85.2)	19 (59.4)	12 (48.0)	11 (45.9)	13 (52.0)	20 (66.7)	19 (53.3)	20 (64.6)	18 (60.0)	76 (52.4)	39 (67.3)

Trial	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66, 68] (n=95)			M14-868 (SURVEYOR-II, Part 1)[59, 60, 64, 69] (n=195)							M14-868 (SURVEYOR-II, Part 4)[59, 64, 65] (n=203)	
Baseline characteristic, n (%)	**GT1 NC G/P (300 mg/120 mg) 8 weeks (n=34)**	**GT1 CC G/P (200 mg/120 mg) 12 weeks (n=27)**	**GT4, GT5, GT6 NC G/P (300 mg/120 mg) 12 weeks (n=32)[a]**	**GT2 G/P (300 mg/120 mg) 12 weeks (n=25)**	**GT2 G/P (200 mg/120 mg) 12 weeks (n=24)**	**GT2 G/P (200 mg/120 mg) + RBV 12 weeks (n=25)**	**GT3 G/P (300 mg/120 mg) 12 weeks (n=30)**	**GT3 G/P (200 mg/120 mg) 12 weeks (n=30)**	**GT3 G/P (200 mg/120 mg) + RBV 12 weeks (n=31)**	**GT3 G/P (200 mg/40 mg) 12 weeks (n=30)**	**GT2 G/P 8 weeks (n=145)**	**GT4, GT5, or GT6 G/P 8 weeks (n=58)**
CT	-	-	-	9 (36.0)	7 (29.2)	9 (36.0)	18 (60.0)	16 (53.3)	14 (45.2)	9 (30.0)	56 (38.6)	28 (48.3)
TT	-	-	-	3 (12.0)	4 (16.7)	4 (16.0)	2 (6.7)	3 (10.0)	6 (19.4)	9 (30.0)	20 (13.8)	11 (19.0)
Baseline HCV RNA level (IU/mL)												
Category 1: <6,000,000	21 (61.8)	15 (55.6)	20 (62.5)	9 (36.0)	9 (37.5)	8 (32.0)	13 (43.3)	16 (53.3)	17 (54.8)	19 (63.3)	83 (57.2)	49 (84.5)
Category 1: ≥6,000,000	13 (38.2)	12 (44.4)	12 (37.5)	16 (64.0)	15 (62.5)	17 (68.0)	17 (56.7)	14 (46.7)	14 (45.2)	11 (36.7)	62 (42.8)	9 (15.5)
Category 2: <10,000,000	-	-	-	12 (48.0)	11 (45.8)	10 (40.0)	18 (60.0)	21 (70.0)	21 (67.7)	21 (70.0)	107 (73.8)	50 (86.2)
Category 2: ≥10,000,000	-	-	-	13 (52.0)	13 (54.2)	15 (60.0)	12 (40.0)	9 (30.0)	10 (32.3)	9 (30.0)	38 (26.2)	8 (13.8)

[a]As described in Appendix Section D.1.2.2.5, 2 patients enrolled in this arm actually received G/P at a dose of 200 mg/120 mg, and were included in an arm in Part 1 for safety analysis (not described in this submission) and in this arm in Part 2 for efficacy analysis. Baseline characteristics for this arm are reported for the 32 patients that received the correct treatment; [b]This patient had a protocol deviation

Abbreviations: BMI, body mass index; CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IL28B, interleukin-28b; NC, non-cirrhotic; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir

Table 19: HCV genotypes and subtypes of participants in the SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 trials

Trial	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66, 68] (n=95)			M14-868 (SURVEYOR-II, Part 1)[59, 60, 64, 69] (n=195)							M14-868 (SURVEYOR-II, Part 4) [59, 64, 65] (n=203)	
GT, n (%)	GT1 NC G/P (300 mg/120 mg) 8 weeks (n=34)	GT1 CC G/P (200 mg/120 mg) 12 weeks (n=27)	GT4, GT5, GT6 NC G/P (300 mg/120 mg) 12 weeks (n=32)[b]	GT2 G/P (300 mg/120 mg) 12 weeks (n=25)	GT2 G/P (200 mg/120 mg) 12 weeks (n=24)	GT2 G/P (200 mg/120 mg) + RBV 12 weeks (n=25)	GT3 G/P (300 mg/120 mg) 12 weeks (n=30)	GT3 G/P (200 mg/120 mg) 12 weeks (n=30)	GT3 G/P (200 mg/120 mg) + RBV 12 weeks (n=31)	GT3 G/P (200 mg/40 mg) 12 weeks (n=30)	GT2 G/P 8 weeks (n=145)[c]	GT4, GT5, or GT6 G/P 8 weeks (n=58)
1 (total)	34 (100)	27 (100)	-	-	-	-	-	-	-	-	-	-
1a	24 (70.6)	20 (74.1)	-	-	-	-	-	-	-	-	-	-
1b	10 (29.4)	7 (25.9)	-	-	-	-	-	-	-	-	-	-
2 (total)	-	-	-	25 (100)	24 (100)	25 (100)	0	1 (3.3)	-	-	145 (100)	-
2[a]	-	-	-	1 (4.0)	7 (29.2)	1 (4.0)	0	1 (3.3)[d]	-	-	34 (23.4)	-
2a	-	-	-	0	0	0	0	0	-	-	2 (1.4)	-
2a/2c	-	-	-	2 (8.0)	0	2 (8.0)	0	0	-	-	14 (9.7)	-
2b	-	-	-	22 (88.0)	17 (70.8)	22 (88.0)	0	0	-	-	95 (65.5)	-
3 (total)	-	-	-	-	-	-	30 (100)	29 (100)	31 (100)	30 (100)	-	-
3[a]	-	-	-	-	-	-	0	1 (3.3)	1 (3.2)	1 (3.3)	-	-
3a	-	-	-	-	-	-	30 (100)	28 (93.3)	30 (96.8)	29 (96.7)	-	-
4 (total)	-	-	20 (62.5)	-	-	-	-	-	-	-	-	46 (79.3)
4[a]	-	-	-	-	-	-	-	-	-	-	-	19 (32.8)
4f	-	-	-	-	-	-	-	-	-	-	-	1 (1.7)
4h	-	-	-	-	-	-	-	-	-	-	-	3 (5.2)
4m	-	-	-	-	-	-	-	-	-	-	-	1 (1.7)
5 (total)	-	-	1 (3.1)	-	-	-	-	-	-	-	-	2 (3.4)

Trial	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66, 68] (n=95)			M14-868 (SURVEYOR-II, Part 1)[59, 60, 64, 69] (n=195)							M14-868 (SURVEYOR-II, Part 4) [59, 64, 65] (n=203)	
GT, n (%)	GT1 NC G/P (300 mg/120 mg) 8 weeks (n=34)	GT1 CC G/P (200 mg/120 mg) 12 weeks (n=27)	GT4, GT5, GT6 NC G/P (300 mg/120 mg) 12 weeks (n=32)[b]	GT2 G/P (300 mg/120 mg) 12 weeks (n=25)	GT2 G/P (200 mg/120 mg) 12 weeks (n=24)	GT2 G/P (200 mg/120 mg) + RBV 12 weeks (n=25)	GT3 G/P (300 mg/120 mg) 12 weeks (n=30)	GT3 G/P (200 mg/120 mg) 12 weeks (n=30)	GT3 G/P (200 mg/120 mg) + RBV 12 weeks (n=31)	GT3 G/P (200 mg/40 mg) 12 weeks (n=30)	GT2 G/P 8 weeks (n=145)[c]	GT4, GT5, or GT6 G/P 8 weeks (n=58)
5a	-	-	-	-	-	-	-	-	-	-	-	2 (3.4)
6 (total)	-	-	11 (34.4)	-	-	-	-	-	-	-	-	10 (17.2)
6a/6b	-	-	-	-	-	-	-	-	-	-	-	6 (10.3)
6c-1	-	-	-	-	-	-	-	-	-	-	-	2 (3.4)
6e	-	-	-	-	-	-	-	-	-	-	-	1 (1.7)
6l	-	-	-	-	-	-	-	-	-	-	-	1 (1.7)

[a]Subtype could not be determined; [b]As described in D.1.2.2.5, 2 patients enrolled in this arm actually received G/P at a dose of 200 mg/120 mg, and were included in an arm in Part 1 for safety analysis (not described in this submission) and in this arm in Part 2 for efficacy analysis. Baseline characteristics for this arm are reported for the 32 patients that received the correct treatment; [c]Two GT2-infected patients were later determined as GT1 by phylogenetic analysis. These patients were included in the ITT analysis, but were excluded for the comparison to historical threshold; [d]Patient was later found to be infected with HCV GT3a via phylogenetic analysis of baseline RNA
Abbreviations: CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; NC, non-cirrhotic; RBV, ribavirin

B.2.4.2.3 EXPEDITION-1 and SURVEYOR-II, Parts 2 and 3 trials

Baseline characteristics are summarised in Table 20 and genotype distribution in Table 21.

Table 20: Characteristics of participants in the EXPEDITION-1 and SURVEYOR-II, Parts 2 and 3 trials

Trial	M14-172 (EXPEDITION-1)[57] (n=146)	M14-868 (SURVEYOR-II, Part 2)[58-62, 64] (n=163)				M14-868 (SURVEYOR-II, Part 3)[59, 64, 65] (n=131)			
Baseline characteristic, n (%)	G/P 12 weeks (n=146)	GT2 G/P 8 weeks (n=54)	GT3 G/P 8 or 12 weeks (n=53)	GT3 G/P 12 or 16 weeks (n=28)	GT3 G/P + RBV 12 weeks (n=27)	TE-PRS NC G/P 12 weeks (n=22)	TE-PRS NC G/P 16 weeks (n=22)	TN CC G/P 12 weeks (n=40)	TE-PRS CC G/P 16 weeks (n=47)
Age (years)									
Category 1: <65	[redacted]	44 (81.5)	[redacted]	[redacted]	[redacted]	18 (81.8)	19 (86.4)	38 (95.0)	39 (83.0)
Category 1: ≥65	[redacted]	10 (18.5)	[redacted]	[redacted]	[redacted]	4 (18.2)	3 (13.6)	2 (5.0)	8 (17.0)
Category 2: <75	[redacted]	-	[redacted]	[redacted]	[redacted]	-	-	-	-
Category 2: ≥75	[redacted]	-	[redacted]	[redacted]	[redacted]	-	-	-	-
BMI (kg/m^2) <30	[redacted]	43 (79.6)	[redacted]	[redacted]	[redacted]	16 (72.7)	16 (72.7)	25 (62.5)	34 (72.3)
BMI (kg/m^2) ≥30	[redacted]	11 (20.4)	[redacted]	[redacted]	[redacted]	6 (27.3)	6 (27.3)	15 (37.5)	13 (27.7)
Male	90 (61.6)	33 (61.1)	[redacted]	[redacted]	[redacted]	14 (63.6)	14 (63.6)	24 (60.0)	36 (76.6)
Race									
White	120 (82.2)	51 (94.4)	[redacted]	[redacted]	[redacted]	17 (77.3)	20 (90.9)	37 (92.5)	42 (89.4)
Black or African American	[redacted]	1 (1.9)	[redacted]	[redacted]	[redacted]	0	0	0	0
Asian	[redacted]	0	[redacted]	[redacted]	[redacted]	5 (22.7)	2 (9.1)	1 (2.5)	3 (6.4)
Other	[redacted]	2 (3.7)	[redacted]	[redacted]	[redacted]	0	0	2 (5)	2 (4.2)
Baseline fibrosis stage									
F0–F1	-	45 (83.3)	[redacted]	[redacted]	[redacted]	11 (50.0)	15 (68.2)	0	0

Trial	M14-172 (EXPEDITION-1)[57] (n=146)	M14-868 (SURVEYOR-II, Part 2)[58-62, 64] (n=163)				M14-868 (SURVEYOR-II, Part 3)[59, 64, 65] (n=131)			
Baseline characteristic, n (%)	**G/P 12 weeks (n=146)**	**GT2 G/P 8 weeks (n=54)**	**GT3 G/P 8 or 12 weeks (n=53)**	**GT3 G/P 12 or 16 weeks (n=28)**	**GT3 G/P + RBV 12 weeks (n=27)**	**TE-PRS NC G/P 12 weeks (n=22)**	**TE-PRS NC G/P 16 weeks (n=22)**	**TN CC G/P 12 weeks (n=40)**	**TE-PRS CC G/P 16 weeks (n=47)**
F2	-	6 (11.1)	[redacted]	[redacted]	[redacted]	4 (18.2)	2 (9.1)	0	0
F3	-	3 (5.6)	[redacted]	[redacted]	[redacted]	7 (31.8)	5 (22.7)	0	0
F4	-	0	[redacted]	[redacted]	[redacted]	0	0	40 (100)	47 (100)
Baseline Child-Pugh score									
5	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>6	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior HCV treatment history									
Naïve	110 (75.3)	47 (87.0)	[redacted]	[redacted]	[redacted]	0	0	40 (100)	0
Experienced	36 (24.7)	7 (13.0)	[redacted]	[redacted]	[redacted]	22 (100)	22 (100)	0	47 (100)
Type of previous regimen									
IFN-based	[redacted]	-	-	-	-	14 (63.6)	13 (59.1)	0	22 (46.8)
SOF-based	[redacted]	-	-	-	-	8 (36.4)	9 (40.9)	0	25 (53.2)
Type of response to previous treatment									
Breakthrough/ on-treatment non-responder	[redacted]	-	-	-	-	-	-	-	-
Post-treatment relapse	[redacted]	-	-	-	-	-	-	-	-
Unknown/other	[redacted]	-	-	-	-	-	-	-	-

Trial	M14-172 (EXPEDITION-1)[57] (n=146)	M14-868 (SURVEYOR-II, Part 2)[58-62, 64] (n=163)				M14-868 (SURVEYOR-II, Part 3)[59, 64, 65] (n=131)			
Baseline characteristic, n (%)	**G/P 12 weeks (n=146)**	**GT2 G/P 8 weeks (n=54)**	**GT3 G/P 8 or 12 weeks (n=53)**	**GT3 G/P 12 or 16 weeks (n=28)**	**GT3 G/P + RBV 12 weeks (n=27)**	**TE-PRS NC G/P 12 weeks (n=22)**	**TE-PRS NC G/P 16 weeks (n=22)**	**TN CC G/P 12 weeks (n=40)**	**TE-PRS CC G/P 16 weeks (n=47)**
IL28B genotype									
CC	[redacted]	22 (40.7)	[redacted]	[redacted]	[redacted]	7 (31.8)	3 (13.6)	10 (22.7)	20 (50.0)
CT	[redacted]	24 (44.4)	[redacted]	[redacted]	[redacted]	12 (54.5)	15 (68.2)	27 (61.4)	18 (45.0)
Baseline HCV RNA level (IU/mL)									
Category 1: <6,000,000	-	23 (42.6)	[redacted]	[redacted]	[redacted]	13 (59.1)	15 (68.2)	36 (90.0)	37 (78.7)
Category 1: ≥6,000,000	-	31 (57.4)	[redacted]	[redacted]	[redacted]	9 (40.9)	7 (31.8)	4 (10.0)	10 (21.3)
Category 2: <10,000,000	-	37 (68.5)	[redacted]	[redacted]	[redacted]	15 (68.2)	18 (81.8)	39 (97.5)	43 (91.5)
Category 2: ≥10,000,000	-	17 (31.5)	[redacted]	[redacted]	[redacted]	7 (31.8)	4 (18.2)	1 (2.5)	4 (8.5)

[a]At screening, this patient was assessed by the investigator as having cirrhosis but did not end up having qualifying results for cirrhosis per protocol prior to enrolment. The patient did have a historical FibroScan result of 14.0 kPa (F3).
Abbreviations: BMI, body mass index; CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; HCV, hepatitis C virus; IFN, interferon; IL28B, interleukin-28b; IU, infectious unit; NC, non-cirrhotic; peg-IFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN, RBV and/or SOF; TN, treatment-naïve

Table 21: HCV genotypes and subtypes of participants in the EXPEDITION-1 and SURVEYOR-II, Parts 2 and 3 trials

Trial	M14-172 (EXPEDITION-1)[57] (n=146)	M14-868 (SURVEYOR-II, Part 2)[58-62, 64] (n=162)				M14-868 (SURVEYOR-II, Part 3)[59, 64, 65] (n=131)			
GT, n (%)	G/P 12 weeks (n=146)	GT2 G/P 8 weeks (n=54)	GT3 G/P 8 or 12 weeks (n=53)	GT3 G/P 12 or 16 weeks (n=28)	GT3 G/P + RBV 12 weeks (n=27)	TE-PRS NC G/P 12 weeks (n=22)	TE-PRS NC G/P 16 weeks (n=22)	TN CC G/P 12 weeks (n=40)	TE-PRS CC G/P 16 weeks (n=47)
1 (total)	87 (59.6)	-	-	-	-	-	-	-	-
1a	[redacted]	-	-	-	-	-	-	-	-
1b	[redacted]	-	-	-	-	-	-	-	-
2 (total)	34 (23.3)	54 (100)				-	-	-	-
2[a]	[redacted]	8 (14.8)				-	-	-	-
2a	[redacted]	0	-	-	-	-	-	-	-
2a/2c	[redacted]	8 (14.8)	-	-	-	-	-	-	-
2b	[redacted]	38 (70.4)	-	-	-	-	-	-	-
3 (total)	-		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3[a]	-		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3a	-		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3b	-		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3g	-		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 (total)	16 (11.0)	-	-	-	-	-	-	-	-
4[a]	[redacted]	-	-	-	-	-	-	-	-
4a	[redacted]	-	-	-	-	-	-	-	-
4a/4c/4d	[redacted]	-	-	-	-	-	-	-	-
4e	[redacted]	-	-	-	-	-	-	-	-
5 (total)	2 (1.4)	-	-	-	-	-	-	-	-
5a	[redacted]	-	-	-	-	-	-	-	-

Trial	M14-172 (EXPEDITION-1)[57] (n=146)	M14-868 (SURVEYOR-II, Part 2)[58-62, 64] (n=162)				M14-868 (SURVEYOR-II, Part 3)[59, 64, 65] (n=131)			
GT, n (%)	G/P 12 weeks (n=146)	GT2 G/P 8 weeks (n=54)	GT3 G/P 8 or 12 weeks (n=53)	GT3 G/P 12 or 16 weeks (n=28)	GT3 G/P + RBV 12 weeks (n=27)	TE-PRS NC G/P 12 weeks (n=22)	TE-PRS NC G/P 16 weeks (n=22)	TN CC G/P 12 weeks (n=40)	TE-PRS CC G/P 16 weeks (n=47)
6 (total)	7 (4.8)	-	-	-	-	-	-	-	-
6a/6b	[redacted]	-	-	-	-	-	-	-	-
6c-1	[redacted]	-	-	-	-	-	-	-	-

[a]Subtype could not be determined
Abbreviations: CC, compensated cirrhosis; DCV, daclatasvir; G/P, glecaprevir/pibrentasvir (300 mg/ 120 mg); GT, genotype; HCV, hepatitis C virus; NC, non-cirrhotic; peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN, RBV and/or SOF; TN, treatment-naïve

B.2.4.2.4 EXPEDITION-4 and MAGELLAN-I trials

Baseline characteristics are summarised in Table 22 and genotype distribution in Table 23.

Table 22: Characteristics of participants in the EXPEDITION-4 and MAGELLAN-I trials

Trial	M15-462 (EXPEDITION-4)[38, 71] (n=104)	M15-410 (MAGELLAN-I, Part 1)[5, 39, 73] (n=50)			M15-410 (MAGELLAN-I, Part 2)[5, 40, 41, 57, 73] (n=91)	
Baseline characteristic, n (%)	G/P 12 weeks (n=104)	G/P (200 mg/80 mg) 12 weeks (n=6)	G/P (300 mg/120 mg) + RBV 12 weeks (n=22)	G/P (300 mg/120 mg) 12 weeks (n=22)	G/P 12 weeks (n=44)	G/P 16 weeks (n=47)
Age (years)						
Category 1: <65		6 (100)	22 (100)	18 (81.8)	[redacted]	[redacted]
Category 1: ≥65		0	0	4 (18.2)	[redacted]	[redacted]
Category 2: <75	97 (93.3)	-	-	-	-	-
Category 2: ≥75	7 (6.7)	-	-	-	-	-

Trial	M15-462 (EXPEDITION-4)[38, 71] (n=104)	M15-410 (MAGELLAN-I, Part 1)[5, 39, 73] (n=50)			M15-410 (MAGELLAN-I, Part 2)[5, 40, 41, 57, 73] (n=91)	
Baseline characteristic, n (%)	G/P 12 weeks (n=104)	G/P (200 mg/80 mg) 12 weeks (n=6)	G/P (300 mg/120 mg) + RBV 12 weeks (n=22)	G/P (300 mg/120 mg) 12 weeks (n=22)	G/P 12 weeks (n=44)	G/P 16 weeks (n=47)
BMI (kg/m^2) <30	79 (76.0)	4 (66.7)	16 (72.7)	12 (54.5)	30 (68.2)	26 (55.3)
BMI (kg/m^2) ≥30	25 (24.0)	2 (33.3)	6 (27.3)	10 (45.5)	14 (31.8)	21 (44.7)
Male	79 (76.0)	3 (50.0)	20 (90.9)	18 (81.8)	31 (70.5)	33 (70.2)
Race						
White	64 (61.5)	4 (66.7)	17 (77.3)	12 (54.5)	[redacted]	[redacted]
Black or African American	25 (24.0)	2 (33.3)	5 (22.7)	10 (45.5)	[redacted]	[redacted]
Asian	9 (8.7)	0	0	0	[redacted]	[redacted]
Other	6 (5.8)	0	0	0	[redacted]	[redacted]
Baseline fibrosis stage						
F0–F1	[redacted]	4 (66.7)	17 (77.3)	11 (50.0)	[redacted]	[redacted]
F2	[redacted]	1 (16.7)	0	6 (27.3)	[redacted]	[redacted]
F3	[redacted]	1 (16.7)	5 (22.7)	5 (22.7)	[redacted]	[redacted]
F4	[redacted]	0	0	0	[redacted]	[redacted]
Missing	[redacted]	-	-	-	[redacted]	[redacted]
Presence or absence of cirrhosis						
With CC	-	-	-	-	15 (34.1)	12 (25.5)
Without CC	-	-	-	-	29 (65.9)	35 (74.5)
Baseline Child-Pugh score						
5	[redacted]	-	-	-	-	-

Trial	M15-462 (EXPEDITION-4)[38, 71] (n=104)	M15-410 (MAGELLAN-I, Part 1)[5, 39, 73] (n=50)			M15-410 (MAGELLAN-I, Part 2)[5, 40, 41, 57, 73] (n=91)	
Baseline characteristic, n (%)	G/P 12 weeks (n=104)	G/P (200 mg/80 mg) 12 weeks (n=6)	G/P (300 mg/120 mg) + RBV 12 weeks (n=22)	G/P (300 mg/120 mg) 12 weeks (n=22)	G/P 12 weeks (n=44)	G/P 16 weeks (n=47)
6	[redacted]	-	-	-	-	-
>6	[redacted]	-	-	-	-	-
Missing/not applicable	[redacted]	-	-	-	-	-
Prior HCV treatment history						
Naïve	60 (57.7)	-	-	-	-	-
Experienced	44 (42.3)	6 (100)	22 (100)	22 (100)	44 (100)	47 (100)
IFN-based	42 (40.4)	-	-	-	-	-
SOF-based	2 (1.9)	-	-	-	-	-
PI experienced/ NS5A-naïve	-	3 (50.0)	11 (50.0)	11 (50.0)	14 (31.8)	13 (27.7)
NS5A experienced	-	3 (50.0)	11 (50.0)	11 (50.0)	30 (68.2)	34 (72.3)
NS5A experienced PI naïve	-	0	4 (18.2)	4 (18.2)	16 (36.4)	18 (38.3)
NS5A experienced / PI exp-erienced	-	3 (50.0)	7 (31.8)	7 (31.8)	14 (31.8)	16 (34.0)
Type of response to previous treatment						

Trial	M15-462 (EXPEDITION-4)[38, 71] (n=104)	M15-410 (MAGELLAN-I, Part 1)[5, 39, 73] (n=50)			M15-410 (MAGELLAN-I, Part 2)[5, 40, 41, 57, 73] (n=91)	
Baseline characteristic, n (%)	**G/P 12 weeks (n=104)**	**G/P (200 mg/80 mg) 12 weeks (n=6)**	**G/P (300 mg/120 mg) + RBV 12 weeks (n=22)**	**G/P (300 mg/120 mg) 12 weeks (n=22)**	**G/P 12 weeks (n=44)**	**G/P 16 weeks (n=47)**
Breakthrough/ on-treatment non-responder	[redacted]	-	-	-	-	-
Post-treatment relapse	[redacted]	-	-	-	-	-
Unknown/other	[redacted]	-	-	-	-	-
IL28B genotype						
CC	24 (23.1)	2 (33.3)	6 (27.3)	3 (13.6)	[redacted]	[redacted]
Non-CC	80 (76.9)	4 (66.7)	16 (72.7)	19 (86.4)	[redacted]	[redacted]
Missing	-	-	-	-	[redacted]	[redacted]
Baseline HCV RNA level (IU/mL)						
Category 1: <6,000,000	96 (92.3)	6 (100)	11 (50.0)	12 (54.5)	40 (90.9)	38 (80.9)
Category 1: ≥6,000,000	8 (7.7)	0	11 (50.0)	10 (45.5)	4 (9.1)	9 (19.1)
Category 2: <10,000,000	100 (96.2)	-	-	-	42 (95.5)	45 (95.7)
Category 2: ≥10,000,000	4 (3.8)	-	-	-	2 (4.5)	2 (4.3)
CKD stage						
Stage 4 no dialysis	13 (12.5)	-	-	-	-	-

Trial	M15-462 (EXPEDITION-4)[38, 71] (n=104)	M15-410 (MAGELLAN-I, Part 1)[5, 39, 73] (n=50)			M15-410 (MAGELLAN-I, Part 2)[5, 40, 41, 57, 73] (n=91)	
Baseline characteristic, n (%)	**G/P 12 weeks (n=104)**	**G/P (200 mg/80 mg) 12 weeks (n=6)**	**G/P (300 mg/120 mg) + RBV 12 weeks (n=22)**	**G/P (300 mg/120 mg) 12 weeks (n=22)**	**G/P 12 weeks (n=44)**	**G/P 16 weeks (n=47)**
Stage 5 no dialysis	6 (5.8)	-	-	-	-	-
Requiring dialysis	85 (81.7)	-	-	-	-	-
Not applicable	0	6	22	22	[redacted]	[redacted]

[a]Percentages are calculated based on non-missing values (i.e., based on patients with CC)
Abbreviations: BMI, body mass index; CC, compensated cirrhosis; CKD, chronic kidney disease; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; IL28B, interleukin-28b; NC, non-cirrhotic; PI, protease inhibitor; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir[redacted]

Table 23: HCV genotypes of participants in the EXPEDITION-4 and MAGELLAN-I trials

Trial	M15-462 (EXPEDITION-4)[38, 64, 71] (n=104)	M15-410 (MAGELLAN-I, Part 1)[5, 39, 57, 73] (n=50)			M15-410 (MAGELLAN-I, Part 2)[5, 40, 41, 73] (n=91)	
GT, n (%)	**G/P 12 weeks (n=104)**	**G/P (200 mg/80 mg) 12 weeks (n=6)**	**G/P (300 mg/120 mg) + RBV 12 weeks (n=22)**	**G/P (300 mg/120 mg) 12 weeks (n=22)**	**G/P 12 weeks (n=44)**	**G/P 16 weeks (n=47)**
1 (total)	54 (51.9)	6 (100)	22 (100)	22 (100)	43 (97.7)	44 (93.6)
1[a]	1 (1.0)	0	0	0	0	0
1a	23 (22.1)	4 (66.7)	20 (90.9)	18 (81.8)	35 (79.5)	32 (68.1)
1b	29 (27.9)	2 (33.3)	2 (9.1)	4 (18.2)	8 (18.2)	11 (23.4)

Trial	M15-462 (EXPEDITION-4)[38, 64, 71] (n=104)	M15-410 (MAGELLAN-I, Part 1)[5, 39, 57, 73] (n=50)			M15-410 (MAGELLAN-I, Part 2)[5, 40, 41, 73] (n=91)	
GT, n (%)	G/P 12 weeks (n=104)	G/P (200 mg/80 mg) 12 weeks (n=6)	G/P (300 mg/120 mg) + RBV 12 weeks (n=22)	G/P (300 mg/120 mg) 12 weeks (n=22)	G/P 12 weeks (n=44)	G/P 16 weeks (n=47)
1c	0	0	0	0	0	1 (2.1)
1g	1 (1.0)	0	0	0	0	0
2 (total)	17 (16.3)	-	-	-	-	-
2[a]	6 (5.8)	-	-	-	-	-
2a/2c	6 (5.8)	-	-	-	-	-
2b	5 (4.8)	-	-	-	-	-
3 (total)	11 (10.6)	-	-	-	-	-
3a	11 (10.6)	-	-	-	-	-
4 (total)	20 (19.2)	-	-	-	1 (2.3)	3 (6.3)
4[a]	13 (12.5)	-	-	-	0	1 (2.1)
4a/4c/4d	3 (2.9)	-	-	-	0	1 (2.1)
4e	1 (1.0)	-	-	-	1 (2.3)	0
4h	2 (1.9)	-	-	-	0	0
4r	1 (1.0)	-	-	-	0	1 (2.1)
5 (total)	1 (1.0)	-	-	-	-	-
5a	1 (1.0)	-	-	-	-	-
6 (total)	1 (1.0)	-	-	-	-	-
6c-1	1 (1.0)	-	-	-	-	-

[a]Subtype could not be determined
Abbreviations: G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; RBV, ribavirin

B.2.4.2.5 Additional trials

In CERTAIN-1 sub-study 1, demographic characteristics were comparable between the two study arms, with no statistically significant differences between arms for any variable. In sub-study 2, special populations of patients with HCV GT1, 2, and 3 infection were enrolled, including [redacted] CC patients, [redacted] patients with HCV GT3 infection, [redacted] patients who had failed prior DAA therapy, (including [redacted] patients who failed a prior NS5A inhibitor in combination with a PI, [redacted] who failed a prior NS5B inhibitor ["other" previous DAA], and [redacted] who had failed a PI), and [redacted] patients with severe renal impairment at screening, including [redacted] patients with end-stage renal disease requiring hemodialysis.[75]

In CERTAIN-2, demographic characteristics were comparable between treatment arms, with no significant differences between arms for any variable.[78, 80]

B.2.5 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.5.1 Overview of statistical analysis in the relevant trials

The main efficacy analysis set in the randomised controlled trials (RCTs) was the intention-to-treat (ITT) population, defined as all patients who received ≥1 dose of study drug defined based on study arm. The safety population for each trial was defined as all patients who received ≥1 dose of study drug, defined based on actual treatment received (not the arm to which the patient was randomised). Therefore, the efficacy analysis set differed from the safety population in exceptional cases in which a patient enrolled into a particular treatment arm did not receive the correct dose of study drug.

For efficacy endpoints, in general the percentage of patients in the ITT population in each treatment arm (and the difference in rates, if calculated) was summarised with 2-sided 95% confidence intervals, calculated either using the Wilson score method or the normal approximation to the binomial distribution, depending on the study design. Efficacy hypotheses testing for non-inferiority or superiority was performed in ENDURANCE-1, ENDURANCE-2, ENDURANCE-3 and SURVEYOR-II, Part 4; the hypotheses are described in alongside the results in Section B.2.7. In each study, sample sizes were powered to detect the desired difference in treatment effect. Full details of the statistical analyses of each trial can be found in Section B.2.5.2.

B.2.5.2 Summary of statistical analysis in the relevant trials

A summary of the statistical analyses for the relevant trials is provided in Table 24 to Table 27.

B.2.5.2.1 ENDURANCE trials

Table 24: Summary of statistical analysis: ENDURANCE trials

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
Hypothesis objective	The three ranked primary efficacy hypotheses were that: • The SVR12 rate among the ITT-PS (DAA-naïve mono-infected GT1 patients) population receiving G/P for 12 weeks would be non-inferior to the historical SVR12 rate established by current approved SoC regimens for this patient population (OBV/PTV/RTV + DSV ± RBV or SOF/LDV for 12 weeks) • The SVR12 rate among the ITT-PS-PP (all randomised patients in the ITT-PS population, with the exception of patients who prematurely discontinued prior to	The primary efficacy hypothesis was that the rate of SVR12 in the ITT population receiving G/P during the DB treatment period, excluding patients who previously failed treatment with SOF, in combination with RBV ± peg-IFN, would be non-inferior to the 95% SVR12 rate of the current SoC (SOF + RBV for 12 weeks)	The primary efficacy hypotheses were that: • The SVR12 rate among the ITT population receiving G/P for 12 weeks would be non-inferior to the SoC arm (SOF + DCV) • The SVR12 rate among the ITT population receiving G/P for 8 weeks would be non-inferior to the G/P 12-week arm	No formal hypothesis was tested

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
	Week 8, patients who experienced virologic failure prior to Week 8, and patients who had no HCV RNA value in the SVR12 visit window or later) population receiving G/P for 8 weeks would be non-inferior to the SVR12 rate for 12 weeks of treatment with G/P • The SVR12 rate among the ITT-PS population receiving G/P for 8 weeks would be non-inferior to the SVR12 rate for 12 weeks of treatment with G/P			
Statistical analysis of primary endpoint	A fixed sequence testing procedure was used for the ranked primary efficacy endpoints; only if success had been demonstrated for the first primary endpoint did the testing proceed to the second primary endpoint. Similarly, only if success had been demonstrated for the second primary endpoint did the testing proceed to the third primary endpoint:	Non-inferiority was demonstrated if the LCB of the 2-sided 95% CI of the percentage of patients achieving SVR12 was >89%. The non-inferiority margin of 6% was computed based on the historical SVR12 rates in HCV GT2-infected patients and chosen because it preserves 68% of the benefit of the SOF + RBV regimen over the previous peg-IFN +	Non-inferiority in SVR12 rate was demonstrated if the LCB for the difference between arms was above the non-inferiority margin of -6%, or if the LCB of SVR12 rate was >92%. This analysis was also conducted in a per protocol population to support the primary comparisons	The number and percentage of patients in the ITT population achieving SVR12 were summarised with a 2-sided 95% CI, calculated using the normal approximation to the binomial distribution. If the SVR12 rate was 100%, then the Wilson score method was used to calculate the CI

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
	• Efficacy of 12-week treatment duration in the ITT-PS population: non-inferiority was demonstrated if the LCB of the 2-sided 95% CI for the percentage of patients achieving SVR12 was >91% • Efficacy of the 8-week treatment duration in the ITT-PS-PP population: non-inferiority in SVR12 to a 12-week treatment duration was demonstrated using a non-inferiority margin of 5% • Efficacy of the 8-week treatment duration in the ITT-PS population: non-inferiority in SVR12 to a 12-week treatment duration was demonstrated using a non-inferiority margin of 5%	RBV SoC regimen. The normal approximation to the binomial distribution was used to calculate the CIs unless the rate for the primary endpoint was 100%, in which case the Wilson score method was used instead		
Statistical analysis of secondary	For the analyses of SVR12, the percentage of patients in each treatment arm (12-week	The secondary efficacy hypothesis was that the rate of SVR12 in the ITT	If non-inferiority of the 12-week G/P regimen to SOF + DCV was demonstrated, then	The percentage of patients meeting each secondary efficacy endpoint was

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
efficacy endpoints	regimen and 8-week regimen) with a 2-sided 95% Wilson score CI and the difference in rates between arms with a 2-sided 95% Wilson score confidence interval was summarised The percentages of patients with on-treatment virologic failure and post-treatment relapse were summarised for each treatment arm in the ITT population and in the ITT-PS population. 2-sided 95% CIs were provided for rates within treatment arms and for the difference between arms	population receiving G/P during the DB treatment period, excluding patients who had previously failed treatment with SOF, in combination with RBV ± peg-IFN, would be superior to the 95% SVR12 rate of the current SoC (SOF + RBV for 12 weeks). Only if success was demonstrated for the primary endpoint did testing proceed to the first secondary endpoint. Superiority was demonstrated if the LCB of the 2-sided 95% CI of the percentage of patients with SVR12 was >95% For the other secondary endpoints outside the fixed-sequence testing procedure, results were presented with 2-sided 95% CIs using the Wilson score method. For on-treatment virologic failure and post-treatment relapse, the study population was the ITT population receiving G/P during the DB treatment period, excluding patients who had previously failed treatment with SOF, in combination with RBV ± peg-IFN. For the percentage of	a superiority hypothesis was tested. Superiority was demonstrated if the LCB for the difference in SVR12 rates between arms was above 0% The other secondary endpoints outside the fixed-sequence testing procedure were summarised for each treatment arm and for differences between arms, with 2-sided 95% CIs provided for rates within treatment arms and for the difference between arms. Wilson score intervals were used for within-arm summaries and for any between-arm summaries	summarised with 2-sided 95% Wilson score intervals

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
		patients who had previously failed treatment with SOF, in combination with RBV ± peg-IFN, achieving SVR12 at 12 weeks after EOT, the study population was the ITT population receiving G/P during the DB treatment period who had previously failed treatment with SOF, in combination with RBV ± peg-IFN		
Statistical analysis of additional efficacy endpoints	The additional endpoints were summarised and analysed for each treatment arm in the ITT population and ITT-PS population The percentage of patients in each treatment arm with a 2-sided 95% Wilson score CI and the difference in rates between arms with a 2-sided 95% Wilson score CI were summarised	The additional endpoints were summarised and analysed for all patients receiving G/P during the DB treatment period, subdivided into TN/IFN-experienced patients, prior SOF + RBV ± peg-IFN failures, and overall The percentage of patients with each endpoint were summarised along with a 2-sided 95% Wilson score CI	The percentage of patients in each treatment arm with a 2-sided 95% Wilson score interval and the (unadjusted) difference in rates with a 2-sided 95% Wilson score interval was summarised for each additional endpoint	The percentage of patients with each endpoint were summarised with a 2-sided 95% Wilson score CI
Sample size, power calculation	A sample size of 270 patients in each treatment group was calculated to provide a power of >90% to demonstrate non-inferiority of the 12-week treatment arm compared to the historical control SVR12 rate (2-sided 95% LCB >91%), and to demonstrate non-inferiority of the 8-week	A sample size of 180 patients in arm A was calculated to provide a power of >90% to demonstrate non-inferiority to a current SoC regimen (2-sided 95% LCB >89%), assuming an SVR12 rate of 96%	A sample size of 230 patients in the G/P 12-week arm and 115 patients in the SOF + DCV arm was calculated to provide a power of >90% to demonstrate non-inferiority of 12 weeks of treatment with G/P to SOF + DCV, with an LCB for the G/P SVR12 rate >92% or with an LCB for the	The number of patients in this study was based on practical considerations in enrolling patients with less common HCV genotypes

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]
	arm to 12-week arm (based on a -5% non-inferiority margin and a 2-sided significance level of 005). This assumed an SVR12 rate of 97% in each arm		between arm difference in SVR12 rates (G/P – SOF + DCV) >-6%, assuming an SVR12 rate of 97% in both arms With a sample size of 115 patients in the G/P 8-week arm, the study had approximately 80% power to demonstrate non-inferiority of the 8-week duration, with the same underlying assumptions The 92% threshold used for the within arm comparison was established by applying the 6% non-inferiority margin to the SVR rate in the ALLY-3 trial.[81] In TN, HCV GT3 patients without cirrhosis, 80/82 (97.6%) achieved SVR, resulting in a threshold of 92% (97.6%–6% = 91.6%)	
Data management, patient withdrawals	A backward imputation method was used to impute missing responses for SVR analyses. Patients with missing HCV RNA data in the analysis window, after imputations, were imputed as a failure. If a patient started another treatment for HCV, then all HCV RNA values for the patient measured on or after the start date of the new HCV treatment were excluded from the analysis, and the patient was considered a failure for summaries of viral response at all time points after the start of the new HCV treatment. If HCV RNA values were missing from the central laboratory but a local laboratory value was present in the appropriate time period, the local laboratory value was used. For PRO questionnaires, no imputation was performed for missing items ***ENDURANCE-2, -3, and -4***: except in the SF-36v2 For patients discontinuing the study drug, patients were monitored for 24 weeks for safety, HCV RNA, and the emergence and persistence of resistant viral variants			

Trial number (acronym)	M13-590 (ENDURANCE-1)[44-46]	M15-464 (ENDURANCE-2)[47-49]	M13-594 (ENDURANCE-3)[50-52]	M13-583 (ENDURANCE-4)[53-55]

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; DB, double-blind; DCV, daclatasvir; EOT, end of treatment; LDV, ledipasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; ITT, intention-to-treat; ITT-PS, ITT mono-infected GT1 DAA-naïve population; ITT-PS-PP, per-protocol ITT-PS population; LCB, lower confidence bound; OBV/PTV/RTV + DSV, ombitasvir/paritaprevir/ritonavir + dasabuvir; PRO, patient reported outcome; RBV, ribavirin; RNA, ribonucleic acid; peg-IFN, pegylated IFN; SoC, standard of care; SF-36v2, SF-36 version 2; SOF, sofosbuvir; SVR, sustained virologic response; TN, treatment-naïve

B.2.5.2.2 SURVEYOR-I, Part 2, and SURVEYOR-II, Parts 2 and 4 trials

Table 25: Summary of statistical analysis: SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 trials

Trial number (acronym)	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66, 68]	M14-868 (SURVEYOR-II, Part 1)[59, 60, 64, 69]	M14-868 (SURVEYOR-II, Part 4)[59, 64, 65]
Hypothesis objective	No formal hypothesis was tested		• The primary efficacy hypothesis was that the SVR12 rate among GT2 DAA-naïve patients without cirrhosis in the ITT population treated with G/P for 12 weeks would be non-inferior to the historical 95% SVR12 rate of the current SoC (SOF + RBV for 12 weeks) • No formal hypothesis was tested for the GT2 population as a whole, nor the GT4, GT5 and GT6 patient population
Statistical analysis of primary endpoint	For each treatment arm, the number and percentage of patients achieving SVR12 in the ITT population were summarised along with a 95% CI using Wilson score interval		For the GT2 DAA-naïve population, non-inferiority to SoC was demonstrated if the LCB of the 2-sided 95% CI of the percentage of patients achieving SVR12 in the ITT population was >89%. For the GT2 population as a whole, and the GT4, GT5 and GT6 patient populations, the number and percentage of patients achieving SVR12 in the ITT population

Trial number (acronym)	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66, 68]	M14-868 (SURVEYOR-II, Part 1)[59, 60, 64, 69]	M14-868 (SURVEYOR-II, Part 4)[59, 64, 65]
			was summarised along with 95% CIs using Wilson score intervals
Statistical analysis of secondary efficacy endpoints	For each treatment arm, the percentage of patients meeting each secondary efficacy endpoint was summarised with 2-sided 95% Wilson score intervals		The percentage of patients meeting each secondary efficacy endpoint was summarised for each arm with 2-sided 95% Wilson score intervals
Statistical analysis of additional efficacy endpoints	The additional efficacy endpoints were summarised descriptively by treatment arm		
Sample size, power calculation	Sample size was not based on a power calculation		A sample size of 90 GT2-infected DAA-naïve patients without cirrhosis was calculated to provide a power of >80% to demonstrate non-inferiority to a current SoC regimen (SOF + RBV for 12 weeks; 2-sided 95% LCB >89%), using a 1-sample test for superiority using ESAT 6.3, assuming an SVR rate of 97%. For the GT4, GT5 and GT6 patients, efficacy was not compared to historical control rates because small sample sizes that would not allow a statistically-powered non-inferiority comparison were anticipated due to the lower prevalence of these genotypes[36]
Data management, patient withdrawals	A backward imputation method was used to impute missing responses for SVR analyses. Patients with missing HCV RNA data in the analysis window, after imputations, were imputed as a failure. If a patient started another treatment for HCV, then all HCV RNA values for the patient measured on or after the start date of the new HCV treatment were excluded from the analysis, and the patient was considered a failure for summaries of viral response at all time points after the start of the new HCV treatment. If HCV RNA values were missing from the central laboratory but a local laboratory value was present in the appropriate time period, the local laboratory value was used. For PRO questionnaires, no imputation was performed for		

Trial number (acronym)	M14-867 (SURVEYOR-I, Part 2)[60, 62, 66, 68]	M14-868 (SURVEYOR-II, Part 1)[59, 60, 64, 69]	M14-868 (SURVEYOR-II, Part 4)[59, 64, 65]
	missing items except in the SF-36v2. For patients discontinuing the study drug, patients were monitored for 24 weeks for safety, HCV RNA, and the emergence and persistence of resistant viral variants		

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; GT, genotype; HCV, hepatitis C virus; ITT, intention-to-treat; LCB, lower confidence bound; RBV, ribavirin; RNA, ribonucleic acid; SoC, standard of care; SF-36v2, SF-36 version 2; SOF, sofosbuvir; SVR, sustained virologic response

B.2.5.2.3 EXPEDITION-1 and SURVEYOR-II, Parts 2 and 3 trials

Table 26: Summary of statistical analysis: EXPEDITION-1 and SURVEYOR-II, Parts 2 and 3 trials

Trial number (acronym)	M14-172 (EXPEDITION-1)[56, 57]	M14-868 (SURVEYOR-II, Part 2)[58-62, 64]	M14-868 (SURVEYOR-II, Part 3)[59, 64, 65]
Hypothesis objective	No formal hypothesis was tested		
Statistical analysis of primary endpoint	The number and percentage of patients in the ITT population achieving SVR12 were summarised with a 2-sided 95% CI, calculated using the normal approximation to the binomial distribution. ***EXPEDITION-1 only:*** If the SVR12 rate was 100%, then the Wilson score method was used to calculate the CI		
Statistical analysis of secondary efficacy endpoints	The percentage of patients meeting each secondary efficacy endpoint was summarised for each arm with 2-sided 95% Wilson score intervals		
Statistical analysis of additional efficacy endpoints	The percentages of patients with each endpoint were summarised with a 2-sided 95% Wilson score CI	The additional efficacy endpoints were summarised descriptively by treatment arm	
Sample size, power calculation	The number of patients in this study was based on practical considerations in enrolling CC patients. In HCV studies where NC and CC patients are included, the number of CC patients tends to be about 20%[82-84] or less of	Sample size was not based on a power calculation	

Trial number (acronym)	M14-172 (EXPEDITION-1)[56, 57]	M14-868 (SURVEYOR-II, Part 2)[58-62, 64]	M14-868 (SURVEYOR-II, Part 3)[59, 64, 65]
	the total sample size. In this study, 175 represents about 20% of patients planned to be enrolled to 12 weeks of G/P treatment in the ENDURANCE studies		
Data management, patient withdrawals	A backward imputation method was used to impute missing responses for SVR analyses. Patients with missing HCV RNA data in the analysis window, after imputations, were imputed as a failure. If a patient started another treatment for HCV, then all HCV RNA values for the patient measured on or after the start date of the new HCV treatment were excluded from the analysis, and the patient was considered a failure for summaries of viral response at all time points after the start of the new HCV treatment. If HCV RNA values were missing from the central laboratory but a local laboratory value was present in the appropriate time period, the local laboratory value was used. For PRO questionnaires, no imputation was performed for missing items except in the SF-36v2. For patients discontinuing the study drug, patients were monitored for 24 weeks for safety, HCV RNA, and the emergence and persistence of resistant viral variants		

Abbreviations: CC, compensated cirrhosis; CI, confidence interval; DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; ITT, intention-to-treat; PRO, patient reported outcome; RNA, ribonucleic acid; SoC, standard of care; SF-36v2, SF-36 version 2; SVR, sustained virologic response

B.2.5.2.4 EXPEDITION-4 and MAGELLAN-I trials

Table 27: Summary of statistical analysis: EXPEDITION-4 and MAGELLAN-I trials

Trial number (acronym)	M15-462 (EXPEDITION-4)[38, 71, 72]	M15-410 (MAGELLAN-I, Part 1)[5, 39, 73, 74]	M15-410 (MAGELLAN-I, Part 2)[5, 40, 41, 73, 74]
Hypothesis objective	No formal hypothesis was tested		
Statistical analysis of primary endpoint	The number and percentage of patients in the ITT population achieving SVR12 were summarised with a 2-sided 95% CI, calculated using the normal approximation to the binomial distribution. If the SVR12 rate was 100%, then the Wilson score method was used to calculate the CI	For each treatment arm, the number and percentage of patients achieving SVR12 in the ITT population were summarised along with a 95% CI using Wilson score interval. In addition, the difference in SVR12 rates between treatment arms was analysed using the stratum adjusted Mantel-Haenszel proportion with a continuity correction for variance, adjusting for each of the randomisation stratum	
Statistical analysis of	The percentage of patients meeting each secondary efficacy endpoint was	For each treatment arm, the percentage of patients meeting each secondary efficacy endpoint was summarised with 2-sided 95% Wilson score intervals	

Trial number (acronym)	M15-462 (EXPEDITION-4)[38, 71, 72]	M15-410 (MAGELLAN-I, Part 1)[5, 39, 73, 74]	M15-410 (MAGELLAN-I, Part 2)[5, 40, 41, 73, 74]
secondary efficacy endpoints	summarised for each arm with 2-sided 95% Wilson score intervals		
Statistical analysis of additional efficacy endpoints	The percentages of patients with each endpoint were summarised with a 2-sided 95% Wilson score CI	The additional efficacy endpoints were summarised descriptively by treatment arm	
Sample size, power calculation	It was planned to enrol approximately 100 patients to this study	Sample size was not based on a power calculation	
Data management, patient withdrawals	A backward imputation method was used to impute missing responses for SVR analyses. Patients with missing HCV RNA data in the analysis window, after imputations, were imputed as a failure. If a patient started another treatment for HCV, then all HCV RNA values for the patient measured on or after the start date of the new HCV treatment were excluded from the analysis, and the patient was considered a failure for summaries of viral response at all time points after the start of the new HCV treatment. If HCV RNA values were missing from the central laboratory but a local laboratory value was present in the appropriate time period, the local laboratory value was used. ***EXPEDITION-4 only:*** For PRO questionnaires, no imputation was performed for missing items except in the SF-36v2. For patients discontinuing the study drug, patients were monitored for 24 weeks for safety, HCV RNA, and the emergence and persistence of resistant viral variants		

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; ITT, intention-to-treat; PRO, patient reported outcome; RNA, ribonucleic acid; SF-36v2, SF-36 version 2; SVR, sustained virologic response

B.2.5.2.5 EXPEDITION-2 and MAGELLAN-II trials

In EXPEDITION-2 and MAGELLAN-II, for the primary efficacy endpoint (SVR12) the percentage of patients in the ITT population was summarised with a 2-sided 95% confidence interval (CI), calculated using the normal approximation to the binomial distribution (or the Wilson score method if the SVR12 rate was 100%). In EXPEDITION-2, the percentage of patients treated with G/P with SVR12 was non-inferior to the 96% SVR12 rate of the current SoC (SOF/LDV for 12 weeks [96%: 321/335][82] or EBR/GZR for 12 weeks [96%; 210/218][85]) if the lower confidence bound (LCB) of the 2-sided 95% CI of the percentage of patients with SVR12 was >90%.[86] In MAGELLAN-II, the percentage of patients treated with G/P achieving SVR12 was non-inferior to the historical 94% SVR12 rate of the current SoC if the LCB of the 2-sided 95% CI was >86%.[87]

B.2.5.2.6 CERTAIN trials

In the CERTAIN-1 trial, to show non-inferiority in SVR12 rates of 8 weeks of treatment with G/P compared to 12 weeks of treatment with OBV/PTV/RTV, a 2-sided 95% CI for the difference in SVR12 rates was calculated using the normal approximation to the binomial distribution in the primary subset population (ITT subset of patients without baseline Y93H polymorphism). If the lower bound of the CI for the difference (G/P – OBV/PTV/RTV) was above the non-inferiority margin of -10%, then G/P was considered non-inferior to OBV/PTV/RTV. For the secondary endpoints, results were summarised along with 95% CIs, where applicable, using the normal approximation to the binomial distribution or the Wilson score methods.[75]

In CERTAIN-2, to show non-inferiority in SVR12 rates of 8 weeks of treatment with G/P compared to 12 weeks of treatment with SOF + RBV, a 2-sided 95% CI for the difference in SVR12 rates was calculated in the ITT population. For the secondary endpoints, results were summarised along with 95% CIs, where applicable, using the normal approximation to the binomial distribution or the Wilson score methods.[78, 80]

B.2.6 *Quality assessment of the relevant clinical effectiveness evidence*

Quality assessments of the AbbVie studies are provided in Appendix D.

B.2.7 *Clinical effectiveness results of the relevant trials*

B.2.7.1 Overview of clinical effectiveness results

As noted previously, it is common that trials for the treatment of HCV are uncontrolled, with licensing granted on the basis of comparison to historical regimens. The results presented in this submission are therefore primarily non-comparative; however, one placebo-controlled and one active-controlled set of comparisons are available and presented.

Many of the trials had populations comprising a mix of TN and TE patients; ITT results are presented in this section and pre-specified analyses stratified by treatment status are presented in Section B.2.8.

Trial results are presented for primarily NC patients and for those trials informing an 8-week treatment duration first, then for CC patients, and finally covering the smaller trials in specific subpopulations of interest, i.e. HIV co-infection, CKD, DAA-failures and post-transplant patients.

The main results presented for each trial are the primary outcome (SVR12) and secondary outcomes as per the trial protocol, the other additional trial outcomes are provided as appendices, whilst pharmacokinetic data (where a specified trial outcome) are not reported in this submission.

SVR12 (ITT population) summary

The list below is a summary of the SVR12 rates from the G/P trials described in detail in the next sections. The SVR12 rates from each trial are reported whenever possible from ITT patient subpopulations defined by genotype, treatment history and cirrhosis status (the factors upon which NICE has historically based treatment recommendations), and those highlighted in bold correspond to the (anticipated) licensed dose and treatment duration for G/P. SVR12 rates from trials in special populations (e.g. EXPEDITION-2, EXPEDITION-4, MAGELLAN-1 and MAGELLAN-2) are not included in the summary.

GT1

- TN NC
  - ENDURANCE-1[44, 46]: **G/P 8 weeks** [redacted]; G/P 12 weeks [redacted]
  - SURVEYOR-I, Part 2: **G/P 8 weeks 96.6% (28/29)**
- TN CC
  - EXPEDITION-1[57]: **G/P 12 weeks** [redacted]
- TE NC
  - ENDURANCE-1[44, 46]: **G/P 8 weeks** [redacted]; G/P 12 weeks [redacted]
  - SURVEYOR-I, Part 2: **G/P 8 weeks 100% (5/5)**
- TE CC
  - EXPEDITION-1[57]: **G/P 12 weeks** [redacted]

GT2

- TN NC
  - ENDURANCE-2*[47, 49]: G/P 12 weeks [redacted]
  - SURVEYOR-II, Part 4[59, 64, 65]: **G/P 8 weeks** [redacted]
  - SURVEYOR-II, Parts 1 and 2[58-62, 64, 69]: **G/P 8 weeks** [redacted]; G/P 12 weeks [redacted]
- TN CC
  - EXPEDITION-1[57]: **G/P 12 weeks** [redacted]
- TE NC
  - ENDURANCE-2*[47, 49]: G/P 12 weeks [redacted]
  - SURVEYOR-II, Part 4[59, 64, 65]: **G/P 8 weeks** [redacted]
  - SURVEYOR-II, Parts 1 and 2[58-62, 64, 69]: **G/P 8 weeks** [redacted]; G/P 12 weeks [redacted]
- TE CC
  - EXPEDITION-1[57]: **G/P 12 weeks** [redacted]

GT3

- TN NC
  - ENDURANCE-3[52, 88]: **G/P 8 weeks 94.9% (149/157)**; G/P 12 weeks 95.3% (222/233)
  - SURVEYOR-II, Parts 1 and 2[58-62, 64, 69]: G/P 12 weeks [redacted]
- TN CC
  - SURVEYOR-II, Part 2[58-62, 64, 69]: **G/P 12 weeks 100% (24/24**)
  - SURVEYOR-II, Part 3[64, 65]: **G/P 12 weeks 97.5% (39/40)**
- TE NC
  - SURVEYOR-II, Part 3[64, 65]: G/P 12 weeks 90.9% (20/22); **G/P 16 weeks 95.5% (21/22)**
  - SURVEYOR-II, Parts 1 and 2[58-62, 64, 69]: G/P 12 weeks [redacted]
- TE CC
  - SURVEYOR-II, Part 2[58-62, 64]: **G/P 16 weeks** [redacted]
  - SURVEYOR-II, Part 3[64, 65]: **G/P 16 weeks: 95.7% (45/47)**

GT4–6

- TN NC
  - GT4: SURVEYOR-II, Part 4[64]: **G/P 8 weeks** [redacted]
  - GT5: SURVEYOR-II, Part 4[64]: **G/P 8 weeks** [redacted]
  - GT6: SURVEYOR-II, Part 4[64]: **G/P 8 weeks** [redacted]
- TN CC
  - GT4: EXPEDITION-1[57]: **G/P 12 weeks** [redacted]
  - GT5: EXPEDITION-1[57]: **G/P 12 weeks** [redacted]
  - GT6: EXPEDITION-1[57]: **G/P 12 weeks** [redacted]
- TE NC
  - GT4–6: SURVEYOR-II, Part 4[64]: **G/P 8 weeks** [redacted]
- TE CC
  - GT4–6: EXPEDITION-1[57]: **G/P 12 weeks** [redacted]

*ITT population excluding prior SOF+ RBV ± peg-IFN failures

B.2.7.2 Key trials for NC patients, including 8-week treatment duration

B.2.7.2.1 ENDURANCE-1: an 8- or 12-week regimen in GT1 NC patients[44, 46]

The patient population in ENDURANCE-1 was GT1 NC patients, with or without HIV co-infection, who were TN or TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN. Treatment was 12 or 8 weeks of G/P (300 mg/120 mg).

Primary efficacy results: SVR12

Among the ITT mono-infected GT1 NC DAA-naïve population (ITT-PS), the SVR rate 12 weeks after treatment with G/P for 12 or 8 weeks was 99.7% (2-sided 95% CI 99.1% to 100.0%) and 99.1% (2-sided 95% CI 98.1% to 100%), respectively. In the per-protocol ITT-PS population (ITT-PS-PP), the SVR12 rate for treatment with G/P for 12 or 8 weeks was 100% (2-sided 95% CI 98.9% to 100.0%). SVR12 results and non-response are summarised in Table 28. The three ranked primary endpoints were achieved:

- Non-inferiority of the 12-week arm to the historical control (efficacy established by current approved SoC regimens for this patient population [OBV/PTV/RTV + DSV ± RBV or SOF/LDV for 12 weeks]) was demonstrated, as the 95% LCB for SVR12 in the ITT-PS population was >91%
- Non-inferiority of the 8-week arm to the 12-week arm was demonstrated in the ITT-PS-PP population, as the 95% LCB for difference in SVR12 rates was >–5%
- Non-inferiority of the 8-week arm to the 12-week arm was demonstrated in the ITT-PS population, as the 95% LCB for difference in SVR12 rates was >–5%

Table 28: Summary of primary and secondary efficacy results for ENDURANCE-1

Assessment	ITT-PS		ITT-PS-PP	
	G/P 12 weeks (n=332)	G/P 8 weeks (n=335)	G/P 12 weeks (n=331)	G/P 8 weeks (n=332)
SVR12, n/N (%)	331/332 (99.7)	332/335 (99.1)	331/331 (100)	332/332 (100)
95% CI	99.1, 100.0	98.1, 100	98.9, 100.0	98.9, 100.0
Treatment difference (95% CI)	–0.6 (–1.8, 0.6)		0.0 (–1.1, 1.1)	
Non-inferiority threshold	–5%		–5%	
Non-responders, n/N (%)	1/332 (0.3)	3/335 (0.9)	0/331	0/332
Reasons for non-response, n/N (%)				
Virologic failure	0/332	1/335 (0.3)	0/331	0/332
On-treatment	0/332	1/335 (0.3)	0/331	0/332
Relapse	0/332	0/335	0/331	0/332
Non-virologic failure	1/332 (0.3)	2/335 (0.6)	0/331	0/332
Premature study drug discontinuation	0/332	1/335 (0.3)	0/331	0/332
Missing SVR12 data	1/332 (0.3)	1/335 (0.3)	0/331	0/332

Assessment	ITT-PS		ITT-PS-PP	
	G/P 12 weeks (n=332)	G/P 8 weeks (n= 335)	G/P 12 weeks (n=331)	G/P 8 weeks (n= 332)

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention-to-treat; ITT-PS, ITT mono-infected GT1 DAA-naïve population; ITT-PS-PP, per-protocol ITT-PS population; SVR, sustained virologic response

Secondary outcomes

Among the ITT mono-infected GT1 population (ITT-MS) and the ITT population, the SVR12 rates after treatment with G/P for 12 or 8 weeks were 99.7% and 99.1% respectively (Table 29). SVR12 was achieved by 100% of patients with HCV GT1/HIV co-infection and 100% of patients with prior SOF experience in both treatment arms.

In 3 of the 4 non-responders across both treatment arms (Table 28), the reasons for failure to achieve SVR12 in the ITT-PS were non-virologic; one patient experienced on-treatment virologic failure in the 8-week treatment arm.

Table 29: Additional secondary efficacy results for ENDURANCE-1

Assessment	G/P 12 weeks	G/P 8 weeks
SVR12, n/N (%)		
ITT-MS population **95% CI**	333/334 (99.7) (98.3, 99.9)	333/336 (99.1) (97.4, 99.7)
ITT population **95% CI**	351/352 (99.7) (98.4, 99.9)	348/351 (99.1) (97.5, 99.7)
Patients with HCV GT1/HIV co-infection **95% CI**	18/18 (100) (82.4, 100.0)	15/15 (100) (79.6, 100.0)
SOF-experienced HCV GT1-infected patients **95% CI**	2/2 (100) (34.2, 100.0)	1/1 (100) (20.7, 100.0)

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention-to-treat; ITT-MS, ITT mono-infected GT1 population; SOF, sofosbuvir; SVR, sustained virologic response

Conclusions

- In HCV GT1-mono-infected, TE but DAA-naïve patients without cirrhosis, a 12-week regimen of G/P (300 mg/120 mg) OD achieved high efficacy (SVR12 rate of 99.7%), which demonstrated non-inferiority to the current SoC (OBV/PTV/RTV+ DSV ± RBV or SOF/LDV for 12 weeks).
- The SVR12 rate (99.1%) of the 8-week regimen of G/P (300 mg/120 mg) was non-inferior to that of the 12-week regimen.
- Only 1 patient among 703 patients in the study (0.1%) experienced virologic failure and there were no relapses. A similarly high (100%) SVR12 rate was achieved in HCV GT1/HIV-1 co-infected patients treated with G/P (300 mg/120 mg) for 8 weeks or 12 weeks.
- High efficacy was observed regardless of baseline host or viral factors: no significant association was detected between SVR12 and any of the subgroup variables tested (see Section E), including baseline polymorphisms in NS3 and/or NS5A (see Appendix Section D.4.1.1).
- [redacted] from baseline in the EQ-5D-3L Health Index score was observed in either treatment arm (see Appendix Section D.4.1.1).

B.2.7.2.2 ENDURANCE-2: a 12-week regimen in GT2 NC patients[47, 49]

The patient population in ENDURANCE-2 was GT2 NC patients who were TN or TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN. Treatment was 12 weeks of G/P at a dose of 300 mg/120 mg.

Primary efficacy results: SVR12

SVR12 was achieved by 99.5% of the GT2 NC ITT patient population, excluding patients who had previously failed treatment with SOF, in combination with RBV ± peg-IFN, who were treated with G/P for 12 weeks during the double-blinded (DB) treatment period (2-sided 95% CI of 98.5% to 100.0%). SVR12 results and non-response are summarised in Table 30.

The LCB of the 2-sided 95% CI was above 89% (non-inferiority threshold). Therefore, non-inferiority of the SVR12 rate in this patient population to the historical control rate for the SoC regimen (SOF + RBV for 12 weeks) was demonstrated.

Table 30: Summary of primary and secondary efficacy results for ENDURANCE-2

Assessment	ITT excluding patients who had previously failed treatment with SOF, in combination with RBV ± peg-IFN G/P 12 weeks DB (n=196)
SVR12, n/N (%)	195/196 (99.5)
95% CI	98.5, 100.0
Non-responders, n/N (%)	1/196 (0.5)
Reasons for non-response, n/N (%)	
Virologic failure	0/196
Non-virologic failure	1/196 (0.5)
Missing SVR12 data	1/196 (0.5)

Abbreviations: CI, confidence interval; DB, double-blind; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); ITT, intention-to-treat; peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response

Secondary outcomes

The LCB of the 2-sided 95% CI for SVR12 in the ITT patient population, excluding patients who had previously failed treatment with SOF in combination with RBV ± peg-IFN, who were treated with G/P for 12 weeks in the DB treatment period was >95% (superiority threshold). Therefore, the superiority of the SVR12 rate in this patient population, excluding prior SOF + RBV ± peg-IFN failures, to the historical control rate for the SoC regimen (SOF + RBV for 12 weeks) was demonstrated. In the ITT population excluding patients who had previously failed treatment with SOF, in combination with RBV ± peg-IFN, only 1 patient was considered a non-responder, due to missing SVR12 data (Table 30).

Among the ITT population of patients who had previously failed treatment with SOF in combination with RBV ± peg-IFN, who were treated with G/P for 12 weeks in the DB treatment period, the SVR12 rate after treatment with G/P for 12 weeks was 100% (6/6; 2-sided 95% CI 61.0% to 100.0%).

Conclusions

- In HCV GT2-infected patients (excluding patients who had previously failed treatment with SOF, in combination with RBV ± peg-IFN) without cirrhosis who received G/P 300 mg/120 mg OD for 12 weeks, high efficacy was achieved (SVR12 rate of 99.5%; 95% CI 98.5% to 100.0%). This treatment demonstrated non-inferiority and superiority to the historical control rate for the SoC (SOF + RBV for 12 weeks). There were no virologic failures among HCV GT2-infected patients without cirrhosis who received G/P for 12 weeks.

- All HCV GT2-infected TE patients who were prior SOF + RBV ± peg-IFN failures achieved SVR12.
- High efficacy was observed regardless of baseline host or viral factors: no significant association was detected between SVR12 and any of the subgroup variables tested (see Appendix Section E.1.1.2), including baseline polymorphisms in NS3 and/or NS5A (see Appendix Section D.4.1.2).
- At the end of the DB treatment period, there was a trend toward [redacted] from baseline with G/P treatment for 12 weeks compared to placebo in the SF-36v2 mental component summary score. Compared to baseline, at the end of the DB treatment period [redacted] were observed with G/P treatment for 12 weeks in overall work productivity and activity impairment as measured using the WPAI-HCV (see Appendix Section D.4.1.2).

B.2.7.2.3 ENDURANCE-3: an 8- or 12-week regimen in GT3 NC patients[50, 52, 88]

The patient population in ENDURANCE-3 was GT3 NC patients who were TN. Treatment was 12 or 8 weeks of G/P at a dose of 300 mg/120 mg, or 12 weeks of treatment with SOF + DCV.

Primary efficacy results: SVR12

Among the ITT GT3 NC population, the SVR rate 12 weeks after treatment with G/P for 12 or 8 weeks was 95.3% (2-sided 95% CI 92.6% to 98.0%) and 94.9% (2-sided 95% CI 91.5% to 98.3%), respectively. In the same treatment population treated with SOF + DCV for 12 weeks, the SVR12 rate was 96.5% (2-sided 95% CI 93.2% to 99.9%). The SVR12 results and non-response are summarised in Table 31.

In the comparison of G/P treatment for 12 weeks to SOF + DCV treatment for 12 weeks, in the ITT population the LCB of the 95% CI for the treatment difference (G/P – SOF + DCV) was above the non-inferiority margin of -6%, and the LCB of the 95% CI for the SVR12 rate with the G/P arm was greater than 92%. This demonstrates non-inferiority of G/P treatment for 12 weeks to the SoC regimen.

In the comparison of G/P treatment for 12 weeks to G/P treatment for 8 weeks, in the ITT population the LCB of the 95% CI for the treatment difference (12 weeks – 8 weeks) was also above the non-inferiority margin of -6%. This demonstrates non-inferiority of G/P treatment for 12 weeks to the G/P treatment for 8 weeks.

The supportive analysis of SVR12 in the per-protocol ITT population (ITT-PP) [redacted].

Table 31: Summary of primary and secondary efficacy results for ENDURANCE-3

Assessment	ITT		
	G/P 12 weeks (n=233)	SOF + DCV 12 weeks (n=115)	G/P 8 weeks (n=157)
SVR12, n/N (%)	222/233 (95.3)	111/115 (96.5)	149/157 (94.9)
95% CI	92.6, 98.0	93.2, 99.9	91.5, 98.3
Treatment difference (95% CI)	–1.2 (–5.6, 3.1) [G/P 12 weeks vs SOF + DCV 12 weeks]		
Threshold for within G/P 12-week arm	92%		
Non-inferiority threshold	–6%		
Treatment difference (95% CI)	–0.4 (–4.8, 4.0) [G/P 8 weeks vs G/P 12 weeks]		
Threshold for within G/P 8-week arm	92%		

Assessment	ITT		
	G/P 12 weeks (n=233)	SOF + DCV 12 weeks (n=115)	G/P 8 weeks (n=157)
Non-inferiority threshold	–6%		
Non-responders, n/N (%)	11/233 (4.7)	4/115 (3.5)	8/157 (5.1)
Reasons for non-response, n/N (%)			
Virologic failure	4/233 (1.7)	1/115 (0.9)	6/157 (3.8)
On-treatment	1/233 (0.4)	0/115	1/157 (0.6)
Relapse	3/222 (1.4)	1/114 (0.9)	5/150 (3.3)
Non-virologic failure	7/233 (3.0)	3/115 (2.6)	2/157 (1.3)
Premature study drug discontinuation	4/233 (1.7)	1/115 (0.9)	0/157
Missing SVR12 data	3/233 (1.3)	2/115 (1.7)	2/157 (1.3)
	ITT-PP		
Assessment	G/P 12 weeks (n=230)	SOF + DCV 12 weeks (n=113)	
SVR12, n/N (%)	[redacted]	[redacted]	
95% CI	[redacted]	[redacted]	
Treatment difference (95% CI)	[redacted]		
Threshold for within G/P 12-week arm	[redacted]		
Non-inferiority threshold	[redacted]		

Abbreviations: CI, confidence interval; DCV, daclatasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); ITT, intention-to-treat; SOF, sofosbuvir; SVR, sustained virologic response

Secondary outcomes

Superiority of treatment with G/P for 12 weeks to SOF + DCV treatment for 12 weeks

[redacted]

In the group receiving G/P for 12 weeks, 4 patients did not respond due to virologic failure: 1 due to on-treatment failure and 3 due to relapse. In the group receiving SOF + DCV, 1 patient experienced virologic failure due to relapse. In the group receiving G/P for 8 weeks, 6 patients did not respond due to virologic failure: 1 due to on-treatment failure and 5 due to relapse (Table 31).

Conclusions

- Treatment with G/P (300 mg/ 120 mg OD) for 8 or 12 weeks achieved a 94.9% and 95.3% SVR12 rate, respectively, in the ITT population.
- G/P for 12 weeks was non-inferior to SOF + DCV OD by analysis of both ITT and per protocol populations.

- G/P for 8 weeks was non-inferior to 12 weeks by analysis of both ITT and per protocol populations.
- The rates of relapse were 3%, 1%, and 1% in the 8-week G/P arm, 12-week G/P arm, and SOF + DCV arm, respectively, and there was no statistically significant difference between 8-week and 12-week G/P arms.
- Baseline fibrosis stage of F2 versus F0–F1 and the presence of polymorphisms in both NS3 and NS5A versus no baseline polymorphisms [redacted] (see Section E.1.1.3 and Appendix Section D.4.1.3). Baseline fibrosis stage of F3 compared to F0–F1 was not significantly associated with SVR12.
- Although there were [redacted], at the end of the treatment period, the SF-36v2 summary scores showed [redacted] from baseline to the end of the treatment period were observed in each arm for WPAI-HCV overall work impairment and activity impairment scores (see Appendix Section D.4.1.3).

B.2.7.2.4 ENDURANCE-4: a 12-week regimen in GT4, GT5 and GT6 NC patients[53, 55]

The patient population in ENDURANCE-4 was NC patients with GT4, GT5 or GT6 infection, who were TN or TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN. Treatment was 12 weeks of G/P at a dose of 300 mg/120 mg.

Primary efficacy results: SVR12

SVR12 was achieved by 99.2% of the GT2 NC ITT patient population (2-sided 95% CI 97.6% to 100.0%). SVR12 results and non-response are summarised in Table 32.

Table 32: Summary of primary and secondary efficacy results for ENDURANCE-4

Assessment	ITT G/P 12 weeks (n=121)
SVR12, n/N (%)	120/121 (99.2)
95% CI	97.6, 100.0
Non-responders, n/N (%)	1/121 (0.8)
Reasons for non-response, n/N (%)	
Virologic failure	0/121
Non-virologic failure	1/121 (0.8)
Premature study drug discontinuation	1/121 (0.8)

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); ITT, intention-to-treat; SVR, sustained virologic response

Secondary outcomes

No patients experienced on-treatment virologic failure or post-treatment relapse (Table 32).

Conclusions

- High SVR12 rates (99.2%; 95% CI 97.6% to 100.0%) were observed in HCV GT4-, GT5- and GT6-infected patients without cirrhosis who received G/P 300 mg/120 mg OD for 12 weeks.
- No patients experienced virologic failure.
- One patient, who discontinued after receiving less than 2 weeks of therapy, did not achieve SVR12.

- High SVR12 rates were observed in HCV GT4-, GT5- and GT6-infected patients without cirrhosis, regardless of [redacted], prior treatment history, [redacted] (see Section E.1.1.4 and see Appendix Section D.4.1.4).
- At the end of treatment, [redacted] were observed (see Appendix Section D.4.1.4)

B.2.7.2.5 SURVEYOR-II, Part 4: an 8-week regimen for GT2, GT4, GT5 and GT6 NC patients[59, 64, 65]

The patient population in SURVEYOR-II, Part 4 was GT2, GT4, GT5 or GT6 NC patients, who were TN or TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN. Treatment was 8 weeks of G/P at a dose of 300 mg/120 mg.

Primary efficacy results: SVR12

Among the ITT GT2 NC DAA-naïve population, the SVR rate 12 weeks after treatment with G/P for 8 weeks was 98.5% (2-sided 95% CI 96.5% to 100.0%; Table 33). Non-inferiority of 8 weeks of treatment for DAA-naïve GT2-infected patients to the historical control (SOF + RBV for 12 weeks) was demonstrated, as the 95% LCB for SVR12 was >89%.

Among the ITT population as a whole, the SVR rate 12 weeks after treatment with G/P for 8 weeks was 96.6%. Among the ITT GT2 population, the SVR rate 12 weeks after treatment with G/P for 8 weeks was 97.9% (2-sided 95% CI 94.1% to 99.3%). Among the ITT GT4, GT5 and GT6 population, the SVR rate 12 weeks after treatment with G/P for 8 weeks was 93.1% (2-sided 95% CI 83.6% to 97.3%). SVR12 results and non-response are summarised in Table 33.

Table 33: Summary of primary and secondary efficacy results for SURVEYOR-II, Part 4

Assessment	ITT DAA-naïve population G/P 8 weeks	ITT G/P 8 weeks		
	GT2 (n=137)	GT2, GT4, GT5 and GT6 combined (n=203)	GT2 (n=145)	GT4, GT5 or GT6 (n=58)
SVR12, n/N (%)	135/137 (98.5)	196/203 (96.6)	142/145 (97.9)	54/58 (93.1)
95% CI	96.5, 100.0	NR	94.1, 99.3	83.6, 97.3
Non-responders, n/N (%)	2/137 (1.5)	7/203 (3.4)	3/145 (2.1)	4/58 (6.9)
Reasons for non-response, n/N (%)				
Virologic failure	NR	2/203 (1.0)	2/145 (1.4)	0/58
Relapse	-	2/201 (1.0)	2/144 (1.4)	0/57
Non-virologic failure	NR	5/203 (2.5)	1/145 (0.7)	4/58 (6.9)
Premature study drug discontinuation	-	2/203 (1.0)	1/145 (0.7)	1/58 (1.7)
Missing SVR12 data	-	3/203 (1.5)	0/145	3/58 (5.2)

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; NR, not reported; ITT, intention-to-treat; SVR, sustained virologic response

Secondary outcomes

There were no virologic failures (either on-treatment or relapse) among the GT4-, GT5- or GT 6-infected patients. Two GT2-infected patients relapsed within 12 weeks after completion of treatment.

The SVR rate 4 weeks after treatment with G/P for 8 weeks was [redacted] for each genotype, and is summarised in Table 34.

Table 34: Number and percentage of patients achieving SVR4 in SURVEYOR-II, Part 4

Assessment	ITT G/P 8 weeks	
	SVR4, n/N (%)	95% CI
GT2	[redacted]	[redacted]
GT4	[redacted]	[redacted]
GT5	[redacted]	[redacted]
GT6	[redacted]	[redacted]

Abbreviations: CI, confidence interval; GT, genotype; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ITT, intention-to-treat; SVR, sustained virologic response

Conclusions

- HCV GT2-, 4-, 5-, and 6-infected patients without cirrhosis treated with G/P 300 mg/120 mg OD for 8 weeks achieved high efficacy (SVR12 rate of 97%), with a similarly low relapse rate (1%) to that observed in patients treated for 12 weeks.
- The percentage of GT2-infected DAA-naïve patients without cirrhosis treated with G/P for 8 weeks achieving SVR12 (99%) was non-inferior to that of the current SoC (SOF/RBV for 12 weeks).
- The SVR12 rate among GT4-, GT5- and GT6-infected patients was 93%, with no virologic failures observed.
- [redacted] was detected between SVR12 and any of the subgroup variables analysed. Efficacy was [redacted] prior treatment experience, type of prior treatment experience (IFN- or SOF-based), genotype or and subtype, [redacted] (see Section E.1.1.8 and Appendix Section D.4.1.8).
- At the end of treatment compared to baseline, [redacted] SF-36v2 physical and mental component summary scores, and there was [redacted] as well as a [redacted]. A HCVTSat global satisfaction score of [redacted] at post-treatment week 4 [redacted] with treatment (see Appendix Section D.4.1.8).

B.2.7.3 Additional supportive Phase II trials for NC patients

B.2.7.3.1 SURVEYOR-I, Part 2: an 8- or 12-week regimen for GT1, GT4, GT5 and GT6 patients[60, 62, 66, 68]

The patient population in SURVEYOR-I, Part 2 was NC GT4-, GT5- or GT6-infected patients, and NC and CC GT1-infected patients, all of whom were TN or TE with peg-IFN/RBV. GT1 NC patients were treated with 8 weeks of G/P at a dose of 300 mg/120 mg. GT1 CC patients were treated with 12 weeks of G/P at a dose of 200 mg/120 mg; results from this arm are not reported in this submission. GT4, GT5 and GT5 6 NC patients were treated with 12 weeks of G/P at a dose of 300 mg/120 mg.

Primary efficacy results: SVR12

Among the ITT GT1 NC population, the SVR rate 12 weeks after treatment with G/P for 8 weeks was 97.1% (2-sided 95% CI 85.1% to 99.5%). Among the ITT GT4, GT5, and GT6 NC population, the SVR rate 12 weeks after treatment with G/P for 12 weeks was 100% (2-sided 95% CI 89.8% to 100%). SVR12 results and non-response are summarised in Table 35.

Table 35: Summary of primary and secondary efficacy results for SURVEYOR-I, Part 2

Assessment	ITT	
	GT1 NC G/P 8 weeks (n=34)	GT4, GT5, GT6 NC G/P 12 weeks (n=34)[a]
SVR12, n/N (%)	33/34 (97.1)	34/34 (100)
95% CI	85.1, 99.5	89.8, 100
Non-responders, n/N (%)	1/34 (2.9)	0/34 (0)
Reasons for non-response, n/N (%)		
Virologic failure	0/34	0/34
Non-virologic failure	1/34 (2.9)	0/34
Premature study drug discontinuation	1/34 (2.9)	0/34

[a]2 patients received G/P 200 mg/120 mg for 12 weeks
Abbreviations: CI, confidence interval; glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ITT, intention-to-treat; NC, non-cirrhotic; SVR, sustained virologic response

Secondary outcomes

No patients experienced virologic failure (Table 35). The SVR4 rate was [redacted] for both treatment arms (Table 36).

Table 36: Number and percentage of patients without cirrhosis achieving SVR4 in SURVEYOR-I, Part 2

Treatment	ITT	
	SVR4, n/N (%)	95% CI
GT1 NC G/P 8 weeks	[redacted]	[redacted]
GT4, GT5, GT6 NC G/P 12 weeks[a]	34/34 (100)	89.8, 100.0

[a]2 patients received G/P 200 mg/120 mg for 12 weeks
Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); ITT, intention-to-treat; NC, non-cirrhotic; RBV, ribavirin; SVR, sustained virologic response

Conclusions

- Following treatment with G/P 300 mg/120 mg OD for 8 or 12 weeks, SVR12 rates were greater than 97% in all treatment arms of patients with CHC GT1, GT4, GT5, or GT6 infection following treatment with characteristics such as HCV genotype, fibrosis stage or previous HCV treatment history.
- No patients relapsed after achieving SVR12.
- A [redacted] was achieved across treatment arms in all subgroups analysed (see Section E.1.1.5). Baseline polymorphisms [redacted], but they had no impact on response to treatment (see Appendix Section D.4.1.5).
- At the end of treatment compared to baseline at 12 weeks post-treatment, there was a [redacted]. Patients reported [redacted] of fatigue on functioning and

[redacted] work productivity and activity impairments. The HCVTSat global satisfaction scores [redacted] with treatment (see Appendix Section D.4.1.5).

B.2.7.3.2 SURVEYOR-II, Parts 1 and 2: an 8-, 12-, or 16-week regimen for GT2 and GT3 patients[58-62, 64, 69]

The patient population in SURVEYOR-II, Part 1 was NC GT2- or GT3-infected patients who were TN or TE with peg-IFN/RBV. GT2 patients were treated with 12 weeks of G/P at a dose of 300 mg/120 mg, or 12 weeks of G/P at a dose of 200 mg/120 mg with or without RBV (1,000 mg or 1,200 mg [weight based]). GT3 patients were treated with 12 weeks of G/P at a dose of 300 mg/120 mg or 200 mg/40 mg, or 200 mg/120 mg with or without RBV (1,000 mg or 1,200 mg [weight based]). Results for the 300/120 mg treatment arms are reported here.

SURVEYOR-II, Part 2 included GT2-infected patients without cirrhosis who were TN or TE with peg-IFN/RBV. Treatment was 8 weeks of G/P at a dose of 300 mg/120 mg. GT3 patients without cirrhosis were also treated with 8 weeks (TN) or 12 weeks (TE with peg-IFN/RBV) at a dose of 300 mg/120 mg. Finally, TN CC GT3 patients* were treated with G/P at a dose of 300 mg/120 mg with or without RBV (800 mg) for 12 weeks.

Results for NC patients are reported here; results for CC patients are reported in Section B.2.7.5.1.

Primary efficacy results: SVR12

Among the ITT GT2 NC population, the SVR rate 12 weeks after treatment with G/P for 12 weeks was 96.0% (2-sided 95% CI 80.5% to 99.3%) and with G/P for 8 weeks was 98.1% (2-sided 95% CI 90.2% to 99.5%). SVR12 results and non-response for GT2 patients are summarised in Table 37.

Among the ITT GT3 TN NC population, the SVR rate 12 weeks after treatment with G/P for 12 weeks was 93.3% (2-sided 95% CI 78.7% to 98.2%) and with G/P for 8 weeks was 96.6% (2-sided 95% CI 82.8% to 99.4%). The SVR12 rate was [redacted] in GT3 NC patients with prior experience with regimens containing peg-IFN and/or RBV. SVR12 results and non-response for GT3 patients are summarised in Table 38.

*When SURVEYOR-II, Part 2 enrolment was initiated, both TN and TE-PR GT3-infected CC patients were eligible for enrolment. Enrolment was halted for GT3 TE-PR CC patients based on feedback from the United States Food and Drug Administration. As a result, 4 TE-PR patients randomised to receive G/P for 12 weeks had their treatment duration extended to 16 weeks. Three patients randomised to receive G/P + RBV for 12 weeks continued on the same treatment course.

Table 37: Summary of primary and secondary efficacy results for SURVEYOR-II, Parts 1 and 2: GT2 patients without cirrhosis, TN and TE-PR

Assessment	Part 1 - ITT	Part 2 - ITT
	G/P 12 weeks (n=25)	G/P 8 weeks (n=54)
SVR12, n/N (%)	24/25 (96.0)	53/54 (98.1)
95% CI	80.5, 99.3	90.2, 99.7
Non-responders, n/N (%)	1/25 (4.0)	1/54 (1.9)
Reasons for non-response, n/N (%)		
Virologic failure	0/25	0/54
Non-virologic failure	1/25 (4.0)	1/54 (1.9)
Premature study drug discontinuation	1/25 (4.0)	1/54 (1.9)

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ITT, intention-to-treat; SVR, sustained virologic response; TE-PR, treatment-experienced with regimens containing peg-IFN/RBV; TN, treatment-naïve

Table 38: Summary of primary and secondary efficacy results for SURVEYOR-II, Parts 1 and 2: GT3 patients without cirrhosis, TN and TE-PR

Assessment	Part 1 - ITT	Part 2 - ITT	
	TN and TE-PR	TN	TE-PR
	G/P 12 weeks (n=30)	G/P 8 weeks (n=29)	G/P 12 weeks (n=24)
SVR12, n/N (%)	28/30 (93.3)	28/29 (96.6)	[redacted]
95% CI	78.7, 98.2	82.8, 99.4	[redacted]
Non-responders, n/N (%)	2/30 (6.7)	1/29 (3.4)	[redacted]
Reasons for non-response, n/N (%)			
Virologic failure	1/30 (3.3)	0/29	[redacted]
On-treatment virologic failure	0/30	0/29	[redacted]
Relapse	1/29 (3.4)	0/28	[redacted]
Non-virologic failure	1/30 (3.3)	1/29 (3.4)	[redacted]
Missing SVR12 data	1/30 (3.3)	1/29 (3.4)	[redacted]

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; IFN, interferon; ITT, intention-to-treat; NC, non-cirrhotic; peg-IFN, pegylated IFN; RBV, ribavirin; SVR, sustained virologic response; TE-PR, treatment-experienced with regimens containing peg-IFN/RBV; TN, treatment-naïve

Secondary outcomes

In the GT2 patient population, no patients experienced virologic failure (Table 37). The SVR4 rate was [redacted] for both treatment lengths (Table 39).

In the GT3 NC patient population, none of the TN patients treated with G/P for 8 weeks experienced virologic failure. 1 patient from Part 1 treated with G/P for 12 weeks relapsed, and in the TE group treated with G/P for 12 weeks in Part 2, [redacted] (Table 38). The SVR4 rate was [redacted] for all treatment arms (Table 40).

Table 39: Number and percentage of GT2 patients without cirrhosis, TN and TE-PR, achieving SVR4 in SURVEYOR-II, Parts 1 and 2

Treatment	ITT	
	SVR4, n/N (%)	95% CI
Part 1: G/P 12 weeks	[redacted]	[redacted]
Part 2: G/P 8 weeks	[redacted]	[redacted]

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); IFN, interferon; ITT, intention-to-treat; peg-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response; TE-PR, treatment-experienced with regimens containing peg-IFN/RBV; TN, treatment-naïve

Table 40: Number and percentage of GT3 patients without cirrhosis, TN and TE-PR, achieving SVR4 in the ITT population in SURVEYOR-II, Parts 1 and 2

Treatment		SVR4, n/N (%)	95% CI
TN and TE-PR	G/P 12 weeks	[redacted]	[redacted]
TN	G/P 8 weeks	[redacted]	[redacted]
TE-PR	G/P 12 weeks	[redacted]	[redacted]
TN and TE-PR	G/P + RBV 12 weeks	[redacted]	[redacted]

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); IFN, interferon; ITT, intention-to-treat; peg-IFN, pegylated IFN; RBV, ribavirin; SVR, sustained virologic response; TE-PR, treatment-experienced with regimens containing peg-IFN/RBV; TN, treatment-naïve

Conclusions

- HCV GT2-infected patients without cirrhosis treated with G/P 300 mg/120 mg OD for 8 weeks or 12 weeks achieved high efficacy (SVR12 rates of 96% to 100%), with no virologic failures observed.
- TN GT3-infected patients without cirrhosis receiving G/P for a duration of 12 weeks achieved [redacted] and shortening the treatment duration to 8 weeks for patients without cirrhosis resulted in similarly high efficacy (SVR12 rate of 97%), with no virologic failures observed.
- A [redacted] with the regimen of G/P for 12 weeks was observed in [redacted] with treatment experience compared to those naïve to treatment [redacted].
- Efficacy of G/P was high, regardless of [redacted] for both HCV GT2- and GT3-infected patients, [redacted].
- Among HCV [redacted] patients treated with G/P 300 mg/ 120 mg, [redacted] was observed [redacted] (see Section E.1.1.6). The presence of baseline NS3 and/or NS5A polymorphisms had no impact on treatment outcome in GT2-infected patients. Due to [redacted] of polymorphisms coupled with [redacted] within each arm, trends in impact of baseline polymorphisms on treatment outcome in GT3a-infected patients could not be assessed (Appendix Section D.4.1.6).
- At the end of treatment compared to baseline, for the majority of treatment arms there was [redacted] in SF-36v2 components [redacted] impact of fatigue on functioning, and a [redacted] in work productivity and activity impairments. HCVTSat global satisfaction scores [redacted] indicate [redacted] (see Appendix Section D.4.1.6).

B.2.7.3.3 SURVEYOR-II, Part 3: a 12- or 16-week regimen for GT3 patients[59, 64, 65]

The patient population in SURVEYOR-II, Part 3 was GT3 NC and CC patients. GT3 CC patients who were TN received G/P at a dose of 300 mg/120 mg for 12 weeks; GT3 CC patients with prior experience with IFN, peg-IFN, RBV, and/or SOF received G/P at a dose of 300 mg/120 mg for 16 weeks. GT3 NC patients who were TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN were randomised to receive treatment with G/P at a dose of 300 mg/120 mg for 12 or 16 weeks. The results for NC patients are reported here; the results for CC patients are reported in Section B.2.7.5.1.

Primary efficacy results: SVR12

Among the ITT population, the SVR12 rate after treatment with G/P for 12 weeks was 90.9% (2-sided 95% CI 72.2% to 97.5%) for TE-PRS NC patients and 95.5% (2-sided 95% CI 78.2% to 99.2%) for TE-PRS NC patients treated with G/P for 16 weeks.

SVR12 results and non-response are summarised in Table 41.

Table 41: Summary of primary and secondary efficacy results for NC patients in SURVEYOR-II, Part 3

Assessment	ITT NC	
	TE-PRS G/P 12 weeks (n=22)	TE-PRS G/P 16 weeks (n=22)
SVR12, n/N (%)	20/22 (90.9)	21/22 (95.5)
95% CI	72.2, 97.5	78.2, 99.2
Non-responders, n/N (%)	2/22 (9.1)	1/22 (4.5)
Reasons for non-response, n/N (%)		
Virologic failure	2/22 (9.1)	1/22 (4.5)
On-treatment virologic failure	0/22	0/22
Relapse	2/22 (9.1)	1/22 (4.5)
Non-virologic failure	0/22	0/22
Missing SVR12 data	0/22	0/22

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; IFN, interferon; ITT, intention-to-treat; NC, non-cirrhotic; peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

Secondary outcomes

There were 3 virologic failures among NC patients due to post-treatment relapse (Table 41).

The SVR rate 4 weeks after treatment with G/P for 12 or 16 weeks was [redacted] for each treatment arm, and is summarised in Table 42.

Table 42: Number and percentage of NC patients achieving SVR4 in SURVEYOR-II, Part 3 in the ITT population

Assessment		SVR4, n/N (%)	95% CI
NC	TE-PRS G/P 12 weeks	[redacted]	[redacted]
	TE-PRS G/P 16 weeks	[redacted]	[redacted]

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ITT, intention-to-treat; IFN, interferon; NC, non-cirrhotic; peg-IFN, pegylated IFN; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN

Conclusions

- TE-PRS GT3-infected patients without cirrhosis treated with G/P 300 mg/120 mg OD for 16 weeks achieved high efficacy (SVR12 rate of 95%), with a low rate of relapse (5%). Treatment with the shorter duration of 12 weeks resulted in a slightly lower SVR12 rate (91%) and a slightly higher relapse rate (9%) compared to the 16-week regimen.
- Among TE-PRS GT3-infected patients without cirrhosis treated with G/P for 12 or 16 weeks, efficacy was [redacted] (see Section B.2.7.3.3, and Appendix Section D.4.1.7 for further discussion of baseline polymorphisms). Among TE-PRS patients treated with G/P 300 mg/120 mg for 12 weeks, [redacted] (see Section B.2.7.5.1).
- At the end of treatment compared to baseline, there was a [redacted] of fatigue on functioning, and a [redacted] in work productivity and activity impairments. HCVTSat global satisfaction scores [redacted] with treatment (see Appendix Section D.4.1.7)

B.2.7.4 Key trials for CC patients

B.2.7.4.1 EXPEDITION-1: a 12-week regimen in GT1, GT2, GT4, GT5 and GT6 CC patients[57, 89]

The patient population in EXPEDITION-1 was CC patients with GT1, GT2, GT4, GT5 or GT6 infection, who were TN or TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN. Treatment was 12 weeks of G/P at a dose of 300 mg/120 mg.

Primary efficacy results: SVR12

SVR12 was achieved by 99.3% of the CC ITT patient population (2-sided 95% CI [redacted]). SVR12 results and non-response are summarised in Table 43.

Table 43: Summary of primary and secondary efficacy results for EXPEDITION-1

Assessment	ITT G/P 12 weeks (n=146)
SVR12, n/N (%)	145/146 (99.3)
95% CI	[redacted]
Non-responders, n/N (%)	1/146 (0.7)
Reasons for non-response, n/N (%)	
Virologic failure	1/146 (0.7)
Relapse	1/144 (0.7)
Non-virologic failure	0/146

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); ITT, intention-to-treat; SVR, sustained virologic response

The difference in SVR12 rates for HCV GT1-infected, DAA-naïve, CC patients in this study compared to the SVR12 rate of OBV/PTV/RTV + DSV + RBV of 93% (306/329)[90] was [redacted]

The difference in SVR12 rates for HCV GT2-infected, DAA-naïve, CC patients in this study compared to the SVR12 rate of SOF + RBV of 82% (41/50)[83] [redacted].

Secondary outcomes
One patient experienced post-treatment relapse (Table 43).

Conclusions
- In HCV GT1-, GT2-, GT4-, GT5-, or GT6 infected CC patients, a 12-week regimen of G/P 300 mg/120 mg OD achieved high efficacy (SVR12 rate of 99.3%).
- Twelve weeks of therapy with G/P is an effective treatment regimen for GT1-, GT2-, GT4-, GT5-, or GT6-infected CC patients who are TN or failed prior peg-IFN- or SOF-based regimens.
- [redacted] was detected between SVR12 and any of the subgroup variables analysed, [redacted] (see Section E.1.1.9) and presence of baseline polymorphisms (see Appendix Section D.4.1.9).
- At the end of treatment compared to baseline, there was a [redacted] in SF-36v2 components, EQ-5D-3L health index score and WPAI-HCV activity impairment score; patients also reported [redacted] (see Appendix Section D.4.1.9).

B.2.7.4.2 SURVEYOR-II, Part 3: a 12- or 16-week regimen for GT3 CC patients[59, 64, 65]

The patient population in SURVEYOR-II, Part 3 was GT3 NC and CC patients. GT3 CC patients who were TN received G/P at a dose of 300 mg/120 mg for 12 weeks; GT3 CC patients with prior experience with IFN, peg-IFN, RBV, and/or SOF received G/P at a dose of 300 mg/120 mg for 16 weeks. GT3 NC patients who were TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN were randomised to receive treatment with G/P at a dose of 300 mg/120 mg for 12 or 16 weeks. The results for CC patients are reported here; the results for patients without cirrhosis are reported in Section B.2.7.3.3.

Primary efficacy results: SVR12
Among the ITT TN population, the SVR12 rate after treatment with G/P for 12 weeks was 97.5% (2-sided 95% CI 87.1% to 99.6%) for TN CC patients. Among the ITT TE-PRS population, the SVR12 rate after treatment with G/P for 16 weeks was 95.7% (2-sided 95% CI 85.8% to 98.8%) for CC patients. SVR12 results and non-response are summarised in Table 44.

Table 44: Summary of primary and secondary efficacy results for CC patients in SURVEYOR-II, Part 3

Assessment	ITT CC	
	TN G/P 12 weeks (n=40)	TE-PRS G/P 16 weeks (n=47)
SVR12, n/N (%)	39/40 (97.5)	45/47 (95.7)
95% CI	87.1, 99.6	85.8, 98.8
Non-responders, n/N (%)	1/40 (2.5)	2/47 (4.3)
Reasons for non-response, n/N (%)		
Virologic failure	0/40	2/47 (4.3)
On-treatment virologic failure	0/40	1/47 (2.1)
Relapse	0/39	1/46 (2.2)
Non-virologic failure	1/40 (2.5)	0/47
Missing SVR12 data	1/40 (2.5)	0/47

Assessment	ITT CC	
	TN G/P 12 weeks (n=40)	TE-PRS G/P 16 weeks (n=47)

Abbreviations: CC, compensated cirrhosis; CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; IFN, interferon; ITT, intention-to-treat; peg-IFN, pegylated IFN; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

Secondary outcomes

No TN patients experienced virologic failure. There were 2 virologic failures among TE-PRS patients, 1 due to on-treatment virologic failure and 1 due to relapse (Table 44). The TE-PRS CC patient treated with G/P for 16 weeks that experienced on-treatment virologic failure [redacted].

The SVR rate 4 weeks after treatment with G/P for 12 or 16 weeks was [redacted] for each treatment arm, and is summarised in Table 45.

Table 45: Number and percentage of CC patients achieving SVR4 in SURVEYOR-II, Part 3 in the ITT population

Assessment		SVR4, n/N (%)	95% CI
CC	TN G/P 12 weeks	[redacted]	[redacted]
	TE-PRS G/P 16 weeks	[redacted]	[redacted]

Abbreviations: CC, compensated cirrhosis; CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); IFN, interferon; ITT, intention-to-treat; peg-IFN; pegylated IFN; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve

Conclusions

- GT3 TN CC patients treated with G/P 300 mg/120 mg OD for 12 weeks achieved high efficacy (SVR12 rate of 98%), with no virologic failures observed.
- GT3 TE-PRS CC patients treated with G/P for 16 weeks achieved high efficacy (SVR12 rate of 96%), with a low rate of relapse (2%).
- Among GT3 TN CC patients treated for 12 weeks and GT3 TE-PRS CC patients treated for 16 weeks, [redacted] was observed regardless [redacted]. The only subgroup variable found to have [redacted] (see Section B.2.7.5.1, and Appendix Section D.4.1.7 for further discussion of baseline polymorphisms).
- At the end of treatment compared to baseline, there was [redacted] SF-36v2 components, [redacted] of fatigue on functioning, [redacted] in work productivity and activity impairments. HCVTSat global satisfaction scores [redacted] (see Appendix Section D.4.1.7).

B.2.7.5 Additional supportive Phase II trials for CC patients

B.2.7.5.1 SURVEYOR-II, Part 2: an 8-, 12-, or 16-week regimen for GT2 and GT3 patients[58-62, 64, 69]

The patient population in SURVEYOR-II, Part 2 was GT2-infected patients without cirrhosis who were TN or TE with peg-IFN/RBV. Treatment was 8 weeks of G/P at a dose of 300 mg/120 mg. GT3 patients without cirrhosis were also treated with 8 weeks (TN) or 12 weeks (TE with peg-IFN/RBV) at a dose of 300 mg/120

mg. Finally, TN CC GT3 patients were treated with G/P at a dose of 300 mg/120 mg with or without RBV (800 mg) for 12 weeks. Four CC patients who were randomised to receive G/P at a dose of 300 mg/120 mg had prior treatment experience with peg-IFN and/or RBV; their treatment duration was extended to 16 weeks. Primary and secondary efficacy results for this patient group are reported in Appendix Section D.4.2.1. Three patients randomised to receive G/P + RBV for 12 weeks were TE-PR; these patients continued on the same treatment course, and they were included in the efficacy analysis for this treatment arm.

Results for CC patients are reported here; results for patients without cirrhosis are reported in Section B.2.7.3.2.

Primary efficacy results: SVR12

Among the ITT GT3 TN CC population that received 12 weeks of treatment with G/P, the SVR12 rate was 100% (2-sided 95% CI 86.2% to 100%). SVR12 results and non-response are summarised in Table 46.

Table 46: Summary of primary and secondary efficacy results for SURVEYOR-II, Part 2: GT3 TN CC patients

Assessment	Part 2 - ITT
	G/P 12 weeks (n=24)
SVR12, n/N (%)	24/24 (100)
95% CI	86.2, 100
Non-responders, n/N (%)	0/24
Reasons for non-response, n/N (%)	
Virologic failure	0/24
Non-virologic failure	0/24

Abbreviations: CC, compensated cirrhosis; CI, confidence interval; G/P, glecaprevir/pibrentasvir; GT, genotype; ITT, intention-to-treat; SVR, sustained virologic response; TN, treatment-naïve

Secondary outcomes

[redacted] experienced virologic or non-virologic failure (Table 46). The SVR4 rate was [redacted] (Table 47).

Table 47: Number and percentage of GT3 CC patients achieving SVR4 in the ITT population in SURVEYOR-II, Part 2

Treatment			SVR4, n/N (%)	95% CI
CC	TN	G/P 12 weeks	[redacted]	[redacted]

Abbreviations: CC, compensated cirrhosis; CI, confidence interval; G/P, glecaprevir/pibrentasvir; ITT, intention-to-treat; RBV, ribavirin; SVR, sustained virologic response; TN, treatment-naïve

Conclusions

- GT3 TN CC patients receiving G/P 300 mg/120 mg OD for a duration of 12 weeks achieved high efficacy (SVR12 rate of [redacted])
- Among GT3-infected patients treated with G/P, high efficacy was observed [redacted] (see Section E.1.1.6). Due to [redacted] polymorphisms coupled with [redacted] virologic failures within each arm, trends in impact of baseline polymorphisms on treatment outcome in GT3a-infected patients could not be assessed (Appendix Section D.4.1.6).
- At the end of treatment compared to baseline, for the majority of treatment arms there was [redacted] in SF-36v2 components, [redacted] of fatigue on functioning, and a [redacted]

in work productivity and activity impairments. HCVTSat global satisfaction scores [redacted] with treatment (see Appendix Section D.4.1.6).

B.2.7.6 Key trials for specific subpopulations

B.2.7.6.1 EXPEDITION-4: a 12-week regimen in GT1, GT2, GT3, GT4, GT5 and GT6 patients with renal impairment[38, 71]

The patient population in EXPEDITION-4 was patients with renal impairment. NC and CC patients with GT1, GT2, GT3, GT4, GT5 or GT6 infection were included. Patients were TN or TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN. GT3 patients were only TN. Treatment was 12 weeks of G/P at a dose of 300 mg/120 mg.

Primary efficacy results: SVR12

SVR12 was achieved by 98.1% of the ITT patient population (2-sided 95% CI 95.4% to 100.0%). SVR12 results and non-response are summarised in Table 48.

Table 48: Summary of primary and secondary efficacy results for EXPEDITION-4

Assessment	ITT G/P 12 weeks (n=104)
SVR12, n/N (%)	102/104 (98.1)
95% CI	95.4, 100.0
Non-responders, n/N (%)	2/104 (1.9)
Reasons for non-response, n/N (%)	
Virologic failure	0/104
Non-virologic failure	2/104 (1.9)
Premature study drug discontinuation	1/104 (1.0)
Missing SVR12 data	1/104 (1.0)

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); ITT, intention-to-treat; SVR, sustained virologic response

Secondary outcomes

No patients experienced on-treatment virologic failure or post-treatment relapse (Table 48).

Conclusions

- In patients with CKD Stage 4/5, including patients receiving dialysis, the fixed-dose combination of G/P 300 mg/120 mg OD given for 12 weeks demonstrated high efficacy; the SVR12 rate was 98.1%.
- No patients experienced virologic failure.
- No significant association was detected between SVR12 and [redacted]. Efficacy was consistent regardless of [redacted] (see Section E.1.1.10 and Appendix Section D.4.1.10.
- [redacted] mean changes from baseline were observed in patient reported outcome questionnaires (see Appendix Section D.4.1.10)

B.2.7.6.2 MAGELLAN-I, Part 1: a 12-week regimen for GT1 DAA-failures[5, 39, 73]

This patient population is not within the anticipated licence for G/P. The patient population in MAGELLAN-1, Part 1 was GT1-infected NC patients who had failed a prior anti-HCV DAA-containing regimen, including but not limited to, DCV + SMV, DCV + SOF, asunaprevir (ASV) + DCV, SOF + SMV and OBV/PTV/RTV. Treatment was 12 weeks of G/P at a dose of 300 mg/120 mg, with or without RBV (800 mg). Six patients were enrolled to receive G/P at a dose of 200 mg/80 mg for 12 weeks before a decision was made not to pursue the development of this dose. Data are only reported here for patients treated with 12 weeks of G/P at the licensed dose of 300 mg/120 mg.

Primary efficacy results: SVR12

Among the ITT population, the SVR rate 12 weeks after treatment was 86.4% (2-sided 95% CI 66.7% to 95.3%) with G/P for 12 weeks. SVR12 results and non-response are summarised in Table 49. SVR rates by treatment experience are reported in Table 189 in Section E.1.1.11.

Table 49: Summary of primary and secondary efficacy results for MAGELLAN-I, Part 1

Assessment	ITT
	G/P 12 weeks (n=22)
SVR12, n/N (%)	19/22 (86.4)
95% CI	66.7, 95.3
Non-responders, n/N (%)	3/22 (13.6)
Reasons for non-response, n/N (%)	
Virologic failure	1/22 (4.5)
On-treatment virologic failure	1/22 (4.5)
Relapse	0/21
Non-virologic failure	2/22 (9.1)
Missing SVR12 data	2/22 (9.1)

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); ITT, intention-to-treat; RBV, ribavirin; SVR, sustained virologic response

Secondary outcomes

There was 1 on-treatment virologic failure in the patient population treated with G/P for 12 weeks (Table 49).

The SVR rate 4 weeks after treatment with G/P for 8 weeks was [redacted] (Table 50).

Table 50: Number and percentage of patients achieving SVR4 in MAGELLAN-I, Part 1

	ITT	
Assessment	SVR4, n/N (%)	95% CI
G/P 12 weeks	[redacted]	[redacted]

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); ITT, intention-to-treat; RBV, ribavirin; SVR, sustained virologic response

Conclusions

- There was 1 on-treatment virologic failure in the patient population treated with G/P 300 mg/120 mg OD for 12 weeks. This patient was NS5A inhibitor and NS3/4A PI-experienced.
- Efficacy was not affected by host or viral factors, including previous DAA regimen class (see Section E.1.1.11).

- No clear impact of NS3 and/or NS5A baseline polymorphisms on treatment outcome was observed (see Appendix Section D.4.1.11).

B.2.7.6.3 MAGELLAN-I, Part 2: a 12- or 16-week regimen for GT1, GT4, GT5 and GT6 DAA-failures[5, 40, 41, 57, 73]

This patient population is not within the anticipated licence for G/P. The patient population in MAGELLAN-1, Part 2 was NC and CC patients who had failed a prior HCV DAA-containing regimen, with GT1, GT4, GT5 or GT6 infection. DAA-containing regimens were defined as consisting of NS5A-inhibitors DCV, LDV, or OBV, and/or NS3/4A PIs PTV/RTV, SMV, TVR, or BOC, with or without IFN and/or RBV. Treatment was 12 or 16 weeks of G/P at a dose of 300 mg/120 mg. The original study protocol specified randomisation at a 1:1:1 ratio including an arm with G/P (200 mg/80 mg) for 12 weeks. Enrolment into this arm was stopped after 6 patients enrolled based upon the decision not to pursue the development of this dose.

Primary efficacy results: SVR12

Among the ITT population, the SVR rate 12 weeks after treatment was 88.6% [redacted] with G/P for 12 weeks and 91.5% [redacted] with G/P for 16 weeks. SVR12 results and non-response are summarised in Table 51. SVR rates by treatment experience are reported in Table 190 in Section E.1.1.12.

Table 51: Summary of primary and secondary efficacy results for MAGELLAN-I, Part 2

Assessment	ITT	
	G/P 12 weeks (n=44)	G/P 16 weeks (n=47)
SVR12, n/N (%)	39/44 (88.6)	43/47 (91.5)
95% CI	[redacted]	[redacted]
Non-responders, n/N (%)	5/44 (11.4)	4/47 (8.5)
Reasons for non-response, n/N (%)		
Virologic failure	5/44 (11.4)	4/47 (8.5)
On-treatment virologic failure	1/44 (2.3)	4/47 (8.5)
Relapse	4/43 (9.3)	0/43
Non-virologic failure	0/44	0/47

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); ITT, intention-to-treat; SVR, sustained virologic response

Secondary outcomes

In the group treated with G/P for 12 weeks, there was 1 on-treatment virologic failure and 3 post-treatment relapses. In the group treated with G/P for 16 weeks, 4 patients experienced on-treatment virologic failure.

The SVR rate 4 weeks after treatment with G/P for 8 weeks was [redacted] for each treatment arm, and is summarised in Table 52.

Table 52: Number and percentage of patients achieving SVR4 in MAGELLAN-I, Part 2

Treatment	ITT	
	SVR4, n/N (%)	95% CI
G/P 12 weeks	[redacted]	[redacted]
G/P 16 weeks	[redacted]	[redacted]

Abbreviations: CI, confidence interval; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); ITT, intention-to-treat; RBV, ribavirin; SVR, sustained virologic response

Conclusions

- GT1-, GT4-, GT5- or GT6-infected DAA-experienced patients treated with G/P 300 mg/120 mg OD for 12 weeks or 16 weeks achieved SVR12 rates of 88.6% and 91.5%, respectively. The non-response rate was lower in the 16-week treatment arm (4/47, 8.5%) compared with the 12-week treatment arm (5/44, 11.4%).
- NS5A-naïve/PI-experienced patients had an SVR12 rate of 100%. NS5A- and PI-experienced patients had a higher SVR12 rate with the 16-week treatment duration compared with 12 weeks of treatment (81.3% [13/16] versus 78.6% [11/14]) due to a lower relapse rate in the 16-week arm). NS5A-experienced/PI-naïve patients also had a higher SVR12 rate with the 16 week duration compared to the 12-week duration (94.4% [17/18] versus 87.5% [14/16]), again due to a lower relapse rate in the 16-week arm (see Section E.1.1.12).
- [redacted] SVR12 rates were observed in patients who [redacted] (see Section E.1.1.12).
- Across both arms, patients who were [redacted] had a [redacted] rate of virologic failure compared with [redacted] patients (see Section E.1.1.12), which in turn was associated with [redacted] (see Appendix Section D.4.1.12).
- Across both arms, most patients who were [redacted] had [redacted]. In contrast, the minority of [redacted] patients had [redacted] (see Appendix Section D.4.1.12).

B.2.7.6.4 EXPEDITION-2: an 8- or 12-week regimen for patients with HIV co-infection[42]

The SVR12 rate was 100% (136/136) in patients without cirrhosis treated for 8 weeks. The SVR12 rate in the modified ITT population (the ITT population excluding patients with missing data) of CC patients treated for 12 weeks was 93% (14/15). One patient had on-treatment virologic failure at treatment week 8.

B.2.7.6.5 MAGELLAN-II: a 12-week regimen for patients who have received a liver or renal transplant[43]

The SVR12 rate was 98% (98/100) in patients without cirrhosis treated for 12 weeks. The SVR12 rate in the modified ITT population (the ITT population excluding patients with non-virologic failure) was 99% (98/99). There was 1 virologic failure in a GT3 TN patient who relapsed at post-treatment week 4.

B.2.7.7 Additional trial results

The results from the CERTAIN-1 and CERTAIN-2 trials are aligned with the main trials described in the sections above. In CERTAIN-1, the primary efficacy analysis was the percentage of GT1-infected NC patients in the ITT population of sub-study 1 without Y93H polymorphisms who achieved SVR12. This was 99.1% (2-sided 95% CI 97.2% to 100.0%) following 8 weeks of treatment with G/P.[75, 76] In CERTAIN-2, the SVR rate 12 weeks after treatment with G/P for 8 weeks was 97.8% (2-sided 95% CI 94.7% to 100.0%) among GT2-infected DAA-TN patients without cirrhosis.[78, 80] Further results are presented in Appendix Section B.2.4.2.2.

B.2.8 *Subgroup analysis*

The pre-specified subgroup analyses planned for each trial varied depending on design, but for many trials analysis is provided by prior treatment or cirrhosis status, in line with the structure of recommendations in recent NICE guidance.

Except for in EXPEDITION-4, SURVEYOR-I, Part 2, SURVEYOR-II, Parts 1 and 2 and MAGELLAN-I, Part 1, associations between the subgroup variables listed in Table 53 and SVR12 were explored by fitting a logistic regression model on all patients in a modified ITT population (excluding patients with ineligible HCV genotype according to the central laboratory or phylogenetic analyses and who did not achieve SVR12 for reasons other than virologic failure). In EXPEDITION-4, SURVEYOR-I, Part 2, SURVEYOR-II, Parts 1 and 2 and MAGELLAN-I, Part 1, SVR12 was summarised for each subgroup variable listed in Table 53. For the key trials listed in Section B.2.3.1 in which a single arm enrolled patients who were both TN and TE, or CC and NC, the results of these subgroup analyses are reported in Appendix E. These results have been selected for reporting because NICE treatment guidelines are stratified primarily by treatment history and cirrhosis status. Subgroup results are also reported for special patient populations, such as severity of renal impairment.

Table 53: Subgroup variables analysed for an association with SVR12

• HCV genotype and subtype • Previous HCV treatment history • IL28B genotype • Sex • Age • Race • Ethnicity • Baseline BMI • Baseline HCV RNA level • Baseline fibrosis stage	• Baseline HOMA-IR • Baseline platelet count • Baseline albumin • Baseline creatinine clearance • Baseline eGFR • Geographic region • Country • History of diabetes • History of bleeding disorders • History of depression or bipolar disorder	• History of cardiovascular disease • Baseline metabolic syndrome • Injection drug use • Stable opiate substitution • Use of concomitant PPI medications • DAA compliance • Presence of baseline polymorphisms

• **Except ENDURANCE-3**: Previous HCV treatment history
• EXPEDITION-1 and -4, SURVEYOR-I, Part 2, SURVEYOR-II, Parts 1, 2 and 3, and MAGELLAN-1, Part 2 only:
  ○ Baseline alpha fetoprotein
  ○ Baseline Child-Pugh score
• EXPEDITION-4 and MAGELLAN-1, Part 2 only:
  ○ Presence or absence of CC
• EXPEDITION-1 only:
  ○ Baseline total bilirubin
  ○ Baseline INR
• SURVEYOR-I, Part 2 only:
  ○ Baseline APRI
  ○ Baseline FIB-4 score
• EXPEDITION-4 only:
  ○ CKD stage		

Abbreviations: APRI, aminotransferase/platelet ratio index; BMI, body mass index; CC, compensated cirrhosis; CKD, chronic kidney disease; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; FIB, fibrosis; HCV, hepatitis C virus; HOMA-IR, homeostatic model assessment of insulin resistance; IL28B, interleukin-28b; INR, international normalised ratio; PPI, proton pump inhibitor; RNA, ribonucleic acid; SVR, sustained virologic response

B.2.9 *Meta-analysis*

As the G/P trials presented do not provide direct evidence in comparison to all the relevant comparators in this submission, meta-analyses are not presented and the approach taken to comparative effectiveness is detailed in Section B.2.10.

B.2.10 *Indirect and mixed treatment comparisons*

One G/P trial included an active non-G/P comparator. This trial was conducted in GT3 TN NC patients that compared G/P to SOF/DCV (the ENDURANCE-3 study). As SOF/DCV is one of the comparators to G/P in this subgroup, this trial provides relevant direct head-to-head evidence that was used in the economic model.

There are no other trials comparing G/P directly to any other comparators, and therefore an indirect treatment comparison via the SOF + DCV arm of the ENDURANCE-3 study would have been necessary to derive relative treatment effects for G/P versus other comparators. As presented in Table 54, the only studies that investigated SOF/DCV ± RBV, and that would therefore be candidates to allow ENDURANCE-3 to connect to any wider network, were the ALLY-3, ALLY-3+, Hezode (2017b) and AI444040 studies. However, none of these studies compared SOF/DCV with any other therapies, rendering it infeasible to form a network beyond that of G/P and SOF/DCV.

In addition to this, one trial comparing G/P to a placebo comparator was identified – the ENDURANCE-2 study in GT2 patients. However, in this study patients in the placebo arm were switched to open-label G/P after 12 weeks, and therefore this trial cannot provide a true comparison of SVR12 rates (the key outcome) for G/P versus placebo. As such, this study cannot be reliably used as the basis of any indirect treatment comparison via a shared placebo comparator in the GT2 subgroup.

Table 54: Summary of trial evidence for SOF/DCV identified by the SLR

Trial	Population	Treatment arms providing evidence in GT2 or GT3
ALLY-3+	Patients with CHC GT3 who were TN and TE and had advanced fibrosis or CC	• SOF/DCV+ RBV for 12 weeks • SOF/DCV+ RBV for 16 weeks
ALLY3	Patients with CHC GT3 who were TN and TE and had no decompensated liver disease	• SOF/DCV in TN • SOF/DCV in TE
Hézode (2017b)	Patients with CHC GT3 who were TN	• SOF/DCV for 8 weeks
AI444040	Patients with CHC GT1/2/3 who were TN and NC	• SOF/DCV • SOF/DCV+ RBV

Abbreviations: CC, compensated cirrhosis; CHC, chronic hepatitis C; DCV, daclatasvir; GT, genotype; NC, non-cirrhotic; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve

In conclusion, it is not feasible to form any network between G/P and any relevant comparator therapies. Therefore, the economic model presented in Section B.3 of this submission relies on the direct use of SVR rates as reported by relevant trials of G/P and comparator therapies for the subgroup in question. AbbVie acknowledges that this approach means that the selection of SVR rates from across different trials outside of a network meta-analysis (NMA) framework means that results are open to the same risks of bias as would be associated with observational studies. However, lack of control arms is a very common feature of clinical trials in hepatitis C across DAAs, with placebo-controlled comparisons considered unethical, and the infeasibility of forming a network for comparison is therefore not a feature of the G/P evidence base specifically. Indeed, in the most recent NICE appraisal of a DAA (that of SOF/VEL, TA430) it was acknowledged that NMA was feasible only in two subgroups. For these two subgroups, even though it was technically possible to form a network, this network was associated with such limitations as a result of trial heterogeneity that the NICE Committee agreed that it would be inappropriate for the outputs of the indirect treatment comparison (ITC) to inform the cost-effectiveness model.

Where a network for indirect comparison cannot be established, an alternative to naïve indirect comparisons across single-arm trials is the use of matching-adjusted indirect comparison (MAIC). MAICs provide a transparent and objective method of comparing single-arm trials after assuring the similarity of key populations and definitions. However, there was not considered to be merit in pursuing a MAIC approach in this submission as an alternative to naïve indirect comparison. Firstly, the added inferential value of conducting a MAIC over a naïve comparison between G/P and a relevant comparator therapies is highly limited by the fact that G/P and comparator therapies achieve SVR12 rates approaching 100% in many cases. As such, large sample sizes would be required to detect any statistically significant differences in SVR12 rates, rendering MAICs of highly limited inferential value where large sample sizes are not available for G/P and/or comparators. Furthermore, the ability to conduct MAICs is limited by the availability of baseline characteristics reported by the comparator trials. The majority of publications do not provide the breakdown of baseline patient characteristics at the subgroup level; this is particularly important in HCV, a disease for which treatment options are defined by multiple important factors such as genotype, treatment history and liver status. A MAIC can overcome this by balancing populations at the trial level before comparing rates at the subgroup level, but there is a precision loss compared to the directly balancing patient characteristics at the subgroup level. This limitation further reduces the added inferential value of population adjustment. In conclusion, where efficacy rates approach 100%, sample sizes are in some cases limited and available subgroup-level data are incomplete, as is the case in this submission, the added value that MAIC, or other methods for population adjustment, can provide is limited and hence MAICs were not performed.

Ultimately, the approach taken in this submission of using naïve indirect comparisons to inform treatment effect estimates, although associated with acknowledged limitations, is consistent with the approach frequently seen in appraisals of therapies for the treatment of CHC.

B.2.10.1 Uncertainties in the indirect and mixed treatment comparisons

N/A.

B.2.11 *Adverse reactions*

Safety data for G/P are presented as an integrated summary of the trials presented for licensing. As noted previously, many trials were uncontrolled and therefore the majority of the safety data are non-comparative, although two smaller subsets from two Phase III RCTs do allow comparison with placebo and an active comparator, respectively.

B.2.11.1 Integrated safety summary

The registrational clinical programme to confirm the safety and efficacy of G/P includes six Phase III studies (ENDURANCE-1, ENDURANCE-2, ENDURANCE-3, ENDURANCE-4, EXPEDITION-1, and EXPEDITION-4) as well as two expanded Phase II studies (SURVEYOR-II Parts 3 and 4, and MAGELLAN-1 Part 2) evaluating the combination treatment regimen of G/P OD at the dose of G/P 300 mg/120 mg (as co-formulated tablets) in TN and TE HCV GT1–6 infected NC and CC patients, including patients with CKD Stage 4/5 and patients co-infected with HIV-1. These registrational studies included an active-controlled study (ENDURANCE-3, versus SOF + DCV) and a placebo-controlled study (ENDURANCE-2).

The fixed-dose combination, film-coated, commercial tablet formulation was administered in all registrational studies as 3 tablets, each containing G/P 100 mg/40 mg (total dose 300 mg/120 mg) taken OD with food. In addition to these registrational studies, the integrated safety analysis set (Phase II and III Analysis Set) also includes treatment arms from supportive Phase II studies (SURVEYOR-I, Part 2, SURVEYOR-II, Parts 1 and 2, and MAGELLAN-1, Part 1) using the doses selected for the registrational studies (G/P 300 mg/120 mg

without RBV). These studies used the Phase II formulation of separate G/P 100 mg/40 mg tablets, which was shown to provide comparable exposures of G/P as the coformulation under non-fasting conditions.

The safety data include safety laboratory data; vital sign data; treatment-emergent AEs, defined as any AEs with an onset date after the first dose of study drug and within 30 days after the last dose of study drug, except for the placebo arm of ENDURANCE-2 in the placebo-controlled analysis set. For the placebo arm, treatment-emergent AEs were defined as any events that began or worsened in severity after the first dose of placebo through 30 days after the last dose of placebo and prior to Day 1 of open-label active treatment. Serious adverse events (SAEs) occurring throughout each study up to the database lock were collected. Safety was evaluated based on three analysis sets, as described in Table 55.

Table 55: Clinical summary of safety analysis sets

Analysis set	Description	Study/pooled studies	Summarised treatment group(s) or populations
Placebo-controlled	All randomised patients who received at least 1 dose of study drug	ENDURANCE-2	• G/P[a], 12 weeks • Placebo[b], 12 weeks
Active-controlled	All randomised/enrolled patients who received at least dose of study drug	ENDURANCE-3	• G/P, 8 weeks (non-randomised)[c] • G/P, 12 weeks • SOF + DCV, 12 weeks
Phase II and III[d]	All randomised/ enrolled patients from 21 arms of the Phase II and 3 studies who received at least 1 dose of G/P 300 mg/120 mg OD, without RBV	SURVEYOR-I SURVEYOR-II MAGELLAN-I ENDURANCE-1 ENDURANCE-2[e] ENDURANCE-3 ENDURANCE-4 EXPEDITION-1 EXPEDITION-4	• G/P, any duration • With CKD Stage 4/5[f] • Without CKD Stage 4/5[g] • Total

[a]ENDURANCE-2 Arm A (double-blind treatment period data); [b]ENDURANCE-2 Arm B (double-blind treatment period data); [c]Presentations for the active-controlled analysis set include the 2 randomised arms in ENDURANCE-3: the G/P 300 mg/120 mg 12-week arm and the SOF + DCV arm; [d]Patients who received at least 1 dose of G/0 300 mg/120 mg OD, regardless of formulation, excluding those also administered RBV, were included in the Phase II and 3 analysis set. Treatment arms using a regimen other than G/O 300 mg/120 mg OD without RBV in Phase II studies (SURVEYOR-I, SURVEYOR-II, and MAGELLAN-I) were excluded from the Phase II and III analysis set because the doses administrated in those arms were less than those proposed for approval; [e]ENDURANCE-2 Arm A only; [f]EXPEDITION-4; [g]All studies excluding EXPEDITION-4.
Abbreviations: CKD, chronic kidney disease; DCV, daclatasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); OD, once-daily; RBV, ribavirin; SOF, sofosbuvir

Patients enrolled in EXPEDITION-4 had CKD Stage 4/5, and the majority were on dialysis. Given the severity of the underlying renal disease and its associated comorbidities, the frequency and severity of the AEs in patients enrolled in this study were expected to be higher than in patients enrolled in the other registrational studies. Therefore, statistical summaries for the Phase II and III analysis set were presented in 3 columns:

1. Overall Phase II and III analysis set (N = 2369);
2. Phase II and III analysis set excluding EXPEDITION-4 (N = 2265); and
3. EXPEDITION-4 results alone (N = 104).

In this section, the Phase II and III analysis set is primarily presented excluding EXPEDITION-4 (N = 2265).

Presentations for the active-controlled analysis set include the 2 randomised arms using the same duration in ENDURANCE-3 (the G/P 300 mg/120 mg 12-week arm, and the SOF + DCV 12-week arm) in order to ensure the validity of the safety comparison between regimens.

A comparison of the safety of G/P 300 mg/120 mg across durations was made among patients without cirrhosis using the Phase II and III analysis set excluding EXPEDITION-4 (Appendix Section F.1.5).

Further details can be found in Appendix Section F.1.1.

B.2.11.2 Discussion

The data provide evidence of a favourable risk/benefit profile of the fixed-dose combination of G/P 300 mg/120 mg OD in >2,300 HCV-infected adult patients with compensated liver disease. The clinical programme enrolled a broad HCV population, including patients with and without cirrhosis, patients with advanced renal disease, HIV co-infected patients, and patients who previously failed DAA-based regimens, including NS5A inhibitor-experienced patients. The fixed-dose combination of G/P demonstrated a favourable safety profile across all these populations, with no serious safety signals identified. The safety profile of G/P was similar to placebo and SOF + DCV. Although the frequency of diarrhoea was higher in the active arm than in the placebo arm in the placebo-controlled study, G/P is not associated with an increased frequency of diarrhoea based on the totality of the safety data in the programme and based on exposure-response analysis. The overall frequency of patients experiencing diarrhoea in this large Phase II and III analysis set was low (6.4%), and most patients experienced events that were at most mild in severity ([redacted]%).

No relevant alanine aminotransferase (ALT) elevations leading to discontinuations or associated with GLE exposure were observed. Increases in bilirubin were rarely observed and appeared to be associated with the extent of GLE exposure. As with most other HCV PIs, GLE may increase bilirubin, in most cases with indirect predominance. However, in contrast to other PIs that are moderate/strong uridine glucuronyl transferase 1A1 (UGT1A1) inhibitors, GLE is a weak UGT1A1 inhibitor, which could explain the low frequency of hyperbilirubinemia observed in the programme. Grade 3 increases in bilirubin were rare (0.4%) and without bilirubin-related AEs; none were associated with liver disease progression.

B.2.11.3 Additional studies reporting adverse reactions

There are no studies to be presented that report additional adverse reactions to those reported in the studies listed in Section B.2.2 and summarised above in Section B.2.11.1.

B.2.11.4 Overview of safety

G/P demonstrated a favourable safety profile that was similar to placebo and SOF + DCV, and that was similar across durations of 8, 12, and 16 weeks. G/P was well tolerated across a broad and diverse population of patients, including patients with CC, HIV co-infection, and CKD Stage 4/5. Common study ADRs occurring in ≥5% of patients were headache, fatigue, and nausea. Adverse drug reactions were mostly Grade 1 (mild) in severity. Serious ADRs and ADRs leading to premature study drug discontinuation were rare (≤0.1%).

There were no haematological or blood chemistry findings of concern or considered likely related to treatment. Unlike other currently available PIs, no liver-related toxicities and no cases consistent with drug-induced liver injury were identified within the studied patient population. The safety profile in CC patients was similar to those in NC patients. The safety of G/P was not affected by co-infection with HIV-1, sex, older age (≥65 years), race, ethnicity, obesity, or geographic location. In addition, G/P 300 mg/120 mg OD demonstrated a favourable safety profile in patients with any degree of renal insufficiency, including patients on dialysis.

B.2.12 *Ongoing studies*

At the time of submission, the following studies are ongoing or planned:

- Long term outcomes study – M13-576: "A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy (ABT-493 and/or ABT-530) in Patients Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection"
- Paediatric study – M16-123: "A Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Paediatric Patients With Genotypes 1-6 Chronic Hepatitis C Virus (HCV) Infection"
- Prior AbbVie DAA virologic failure study – M15-942: "An Open-Label, Multicentre Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Combination With Sofosbuvir and Ribavirin in Chronic Hepatitis C (HCV) Infected Patients Who Have Experienced Virologic Failure in AbbVie HCV Clinical Studies (MAGELLAN-3)"
- NC study – M16-133: "Single Arm, Open Label, Multicentre Study to Evaluate the Efficacy and Safety of AbbVie HCV DAAs in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotypes 1-6 Infection and an Aspartate Aminotransferase/Platelet Ratio Index (APRI) ≤1"
- CC study – M16-135: "A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/ Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 4, 5 or 6 Infection and CC"
- GT5 and GT6 study – M16-126: "A Study of Glecaprevir/Pibrentasvir in Adults With Chronic Hepatitis C Virus (HCV) Genotype 5 or 6 Infection"

B.2.13 *Innovation*

G/P is a next-generation, oral, once-daily IFN- and RBV-free DAA regimen with antiviral activity against HCV genotypes 1–6, a high barrier to resistance, and a treatment duration as low as 8 weeks for TN NC patients, who represent the majority of HCV-infected individuals.[31] As such, G/P is an innovative treatment for CHC that has a number of potential benefits compared to existing therapies, as follows:

1) G/P is expected to provide an 8-week DAA regimen for TN NC patients across all major genotypes, enabling virologic cure and cessation of treatment 4 weeks sooner than comparator DAA-based therapies. An 8 week duration of treatment with G/P has been demonstrated to achieve SVR12 rates ≥97% across the clinical trial programme treatment arms with this duration, when considering a modified ITT population (excluding non-virologic failures) of TN and TE (with IFN, peg-IFN ± RBV, or SOF + RBV ± IFN) NC GT1–6 patients.[91]

2) G/P has been awarded PIM status by the Medicines and Healthcare Products Regulatory Agency (MHRA) (see Section 1.3c). To our knowledge, G/P is the only DAA to have received the PIM designation to date, demonstrating that this treatment addresses a clear unmet need for subgroups of patients suffering from CHC in the UK. Furthermore, the MHRA has issued a positive scientific opinion for G/P, enabling G/P to become available to specific CHC patient groups with an unmet need in the UK under EAMS.[7] Such patient groups include:

    - **Patients with GT2, GT3, GT5 or GT6 infection with CKD (Stage 4/5)**. There are currently no licensed treatment options for these patients in the UK.

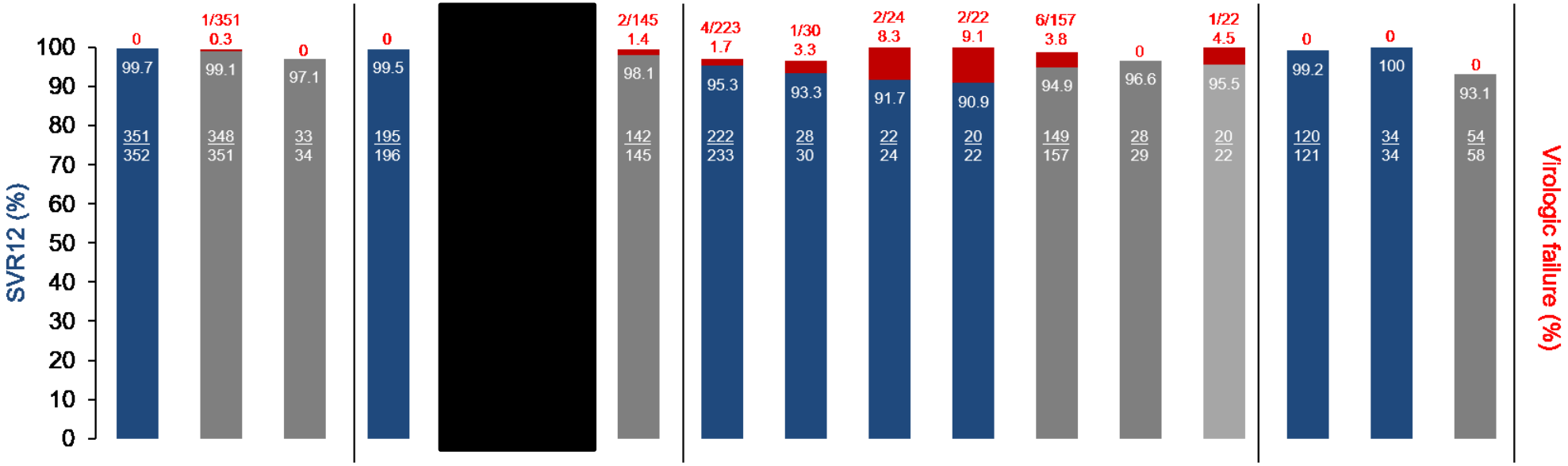
- **Patients with genotype 3 HCV previously treated with peg-IFN, RBV and/or SOF**. Other currently licensed treatments provide suboptimal SVR12 rates in GT3 TE patient populations; for example, the SVR12 rate for SOF/VEL in GT3 TE patients with cirrhosis is <90%.[92]

3) The introduction of G/P may transform how CHC treatment is delivered to patients. As a result of the fact that SOF/VEL is not available to GT2 TN NC IFN-eligible patients, a TN NC patient's genotype must currently be known to initiate an appropriate NICE-recommended treatment. A positive recommendation for G/P in TN NC patients across all 6 major genotypes regardless of IFN-eligibility would remove the need for baseline RAV and viral load testing in patient groups within the anticipated licence, and potentially remove the requirement for genotyping as well, because all TN NC patients within the anticipated licence for G/P would be eligible for an 8-week treatment course of G/P. With a simplified treatment-decision making process and no requirement for genotyping, treatment could be provided to these patients in primary care. Furthermore, the favourable safety profile of G/P (which suggests that minimal monitoring may be required) coupled with its nature as an oral, once-daily regimen with a short treatment duration could enable treatment monitoring to continue in primary care as well. Moving treatment provision into primary care could help to address a barrier to treatment in groups of patients with high prevalence of CHC who are recognised to have difficulty engaging with secondary care services and could therefore benefit from receiving treatment in the community, such as part of an outreach service or at a community pharmacy. This could improve access and adherence to treatment, resulting in better treatment outcomes. Such patient groups include chaotic populations such as PWIDs and patients on opiate substitution therapy, and also South Asian populations.

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

Figure 12 presents a summary of the trial results for NC patients; showing the consistent efficacy of G/P across the subpopulations of HCV. Figure 13 presents a similar summary of the trial results for CC patients. Finally, Figure 14 provides a summary of efficacy in special patient populations. CERTAIN-1 and CERTAIN-2 are not included in this summary due to the limited generalisability of these studies to the UK patient population. It should be noted that results are presented only for treatment arms with a dose of G/P 300 mg/120 mg, as this represents the anticipated licensed formulation of G/P.

Figure 12: Summary of SVR12 results by trial for NC patients[44, 46, 47, 49, 50, 52, 53, 55, 58-62, 64-66, 68-70]

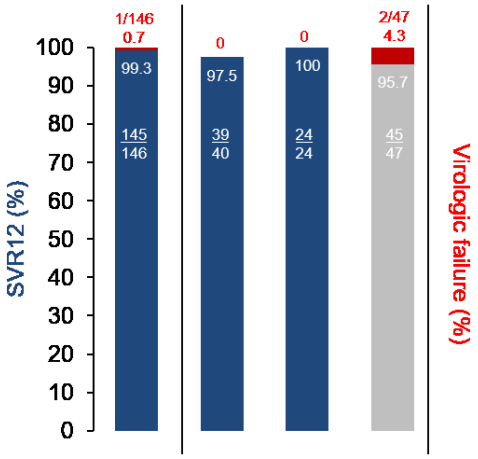


GT	GT1			GT2				GT3							GT4–6		
N[a]	352	351	34	196	[redacted]	[redacted]	145	233	30	24	22	157	29	22	121	34	58
Trial	EN-1[b,c]		S-I P2[b]	EN-2[b,d]	S-II P1[b]	S-II P2[b]	S-II P4[b]	EN-3[e]	S-II P1[f]	S-II P2[g]	S-II P3[h]	EN-3[e]	S-II P2[e]	S-II P3[h]	EN-4[b]	S-I P2[f]	S-II P4[b]
Phase	PIII		PII	PIII	PII			PIII	PII			PIII	PII		PIII	PII	
G/P	G/P 12 wk	G/P 8 wk	G/P 8 wk	G/P 12 wk	G/P 12 wk	G/P 8 wk	G/P 8 wk	G/P 12 wk	G/P 12 wk	G/P 12 wk	G/P 12 wk	G/P 8 wk	G/P 8 wk	G/P 16 wk	G/P 12 wk	G/P 12 wk	G/P 8 wk

[a]ITT population; [b]TN and TE-PRS; [c]Includes patients with HIV-1 co-infection; [d]ITT population from the double-blind treatment period excluding patients who had previously failed treatment with SOF in combination with RBV ± peg-IFN; [e]TN only; [f]TN and TE-PR; [g]TE-PR only; [h]TE-PRS only

Abbreviations: EN, ENDURANCE; G/P, glecaprevir (300 mg)/pibrentasvir (200 mg); GT, genotype; HIV-1, human immunodeficiency virus 1; IFN, interferon; ITT, intention-to-treat; NC, non-cirrhotic; peg-IFN, pegylated IFN; RBV, ribavirin; P, part; PII, Phase II; PIII, Phase III; S, SURVEYOR; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-PR treatment-experienced with regimens containing peg-IFN/RBV; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve; wk, weeks

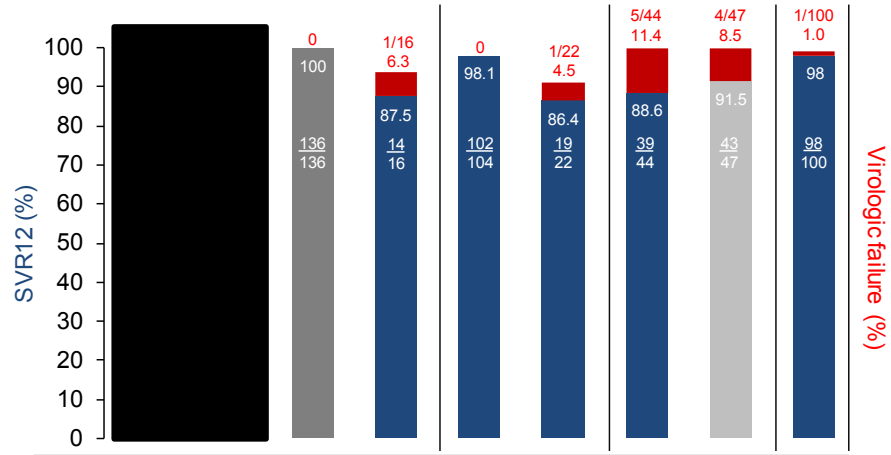
Figure 13: Summary of SVR12 results by trial for CC patients[58-62, 64, 65]



GT	GT1, 2, 4–6	GT3		
N[a]	146	40	24	47
Trial	EX-1[b]	S-II P3[c]	S-II P2[c]	S-II P3[d]
Phase	PIII	PII		
G/P	G/P 12 wk	G/P 12 wk	G/P 12 wk	G/P 16 wk

[a]ITT population; [b]TN and TE-PRS; [c]TN only; [d]TE-PRS only
Abbreviations: CC, compensated cirrhosis; EX, EXPEDITION; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; IFN, interferon; ITT, intention-to-treat; P, Part; peg-IFN, pegylated IFN; PII, Phase II; PIII, Phase III; RBV, ribavirin; S, SURVEYOR; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-PR, treatment-experienced with regimens containing peg-IFN/RBV; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve; wk, weeks

Figure 14: Summary of SVR12 results by trial for special patient populations[38, 39, 42-44, 46, 57, 64]



GT	GT1		GT1–6		GT1–6	GT1	GT1, 4–6		GT1–6
PP	HIV-1 co-infection				CKD	DAA-failures[a]			PLT/ PKT[c]
N[b]	[redacted]	[redacted]	136[c]	16[d]	104	22	44	47	100
Trial	EN-1[c,e]		EX-2[f]		EX-4[g]	M-I P1[c]	M-I P2		M-II
Phase	PIII					PII			PIII
G/P	G/P 12 wk	G/P 8 wk	G/P 8 wk	G/P 12 wk	G/P 12 wk	G/P 12 wk	G/P 12 wk	G/P 16 wk	G/P 12 wk

[a]DAA failures defined as follows: In Part 1: including, but not limited to, DCV + SMV, DCV + SOF, ASV + DCV, SOF + SMV and OBV/PTV/RTV. In Part 2: consisting of NS5A-inhibitors DCV, LDV, or OBV, and/or NS3/4A PIs PTV/RTV, SMV, TVR, or BOC, with or without IFN and/or RBV; [b]ITT population; [c]NC only; [d]CC only; [e]These patients are included in the SVR12 data reported in Figure 12; [f]TN and TE-PRS; [g]TN and TE-PRS except for GT3 (GT3 TN patients only)
Abbreviations: ASV, asunaprevir; BOC, boceprevir; CC, compensated cirrhosis; CKD, chronic kidney disease; DAA, direct-acting antiviral; DCV, daclatasvir; LDV, ledipasvir; EN, ENDURANCE; EX, EXPEDITION; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); HIV-1, human immunodeficiency virus 1; IFN, interferon; ITT, intention-to-treat; M, MAGELLAN; NC, non-cirrhotic; OBV, ombitasvir; P, Part; peg-IFN, pegylated IFN; PI, protease inhibitors; PII, Phase II; PIII, Phase III; PKT, post-kidney transplant; PLT, post-liver transplant; PP, patient population; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TE-PRS, treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve; TVR, telaprevir; wk, weeks

Overall across trials presented at licensing and summarised in this submission, G/P achieved an SVR12 rate of [redacted]%, with a virologic failure rate of [redacted]% in 2369 patients across HCV genotypes, treatment durations, and prior treatment experience, including patients with baseline polymorphisms or comorbidities (CC, renal impairment, and HIV-1 co-infection).[93]

Among the largest HCV population, TN NC patients, the regimen provides high efficacy with treatment duration shorter than most currently approved therapies, particularly in GT2–6. Furthermore, the G/P combination achieved high efficacy in HCV populations with currently limited or no treatment options such as patients with severe renal impairment infected with GT2, GT3, GT5, and GT6. In addition, treatment with G/P for 16 weeks achieved >95% SVR12 rates in GT3 TE CC patients.

The fixed-dose combination of G/P demonstrated a favourable safety profile (see Section B.2.11) in patients treated for 8, 12, or 16 weeks, and across all populations studied. The overall safety profile was similar to that observed in patients receiving placebo or SOF + DCV. The type, frequency, and severity of AEs in CC patients were similar to those in NC patients. In addition, G/P demonstrated a favourable safety profile in patients with severe renal insufficiency, including patients on dialysis.

Overall, G/P is a pan-genotypic and highly effective oral treatment regimen that is well tolerated, addresses several areas of unmet medical need, and offers treatment durations as short as 8 weeks for TN NC patients.

B.3 Cost effectiveness

- A cohort Markov state-transition model was developed to evaluate the cost-effectiveness of G/P for the treatment of CHC from a UK NHS perspective. The model was developed to align closely with previous cost-effectiveness models presented to NICE for treatments for CHC, including that presented in the most recent appraisal in this indication (TA430).
- Patient subgroups presented in the model are defined by HCV genotype, treatment history, fibrosis status and, in the case of GT2 TN patients, IFN-eligibility, totalling 26 subgroups.
- Relevant comparator treatments for each patient subgroup were determined based on consideration of NICE-approved treatments for CHC, expert advice from English clinicians and the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1).[2]
- Treatment characteristics for G/P and comparators (SVR and AE rates, and treatment duration) were derived from the clinical trials identified by the clinical effectiveness SLR.
- Health state utilities were applied from the literature in line with prior appraisals of therapies for HCV. An update to a previous SLR for HRQoL conducted for TA430 found no new studies with utility values that were appropriate to inform the economic analysis.
- The impact of DAA therapies and their associated AEs on patients' HRQoL was captured through application of treatment-related changes in health utility. These were determined for G/P and comparators using EQ-5D utility index scores from the clinical trials identified by the clinical effectiveness SLR.
- Costs and resource use inputs and assumptions were based on UK sources, including NHS reference costs, the British National Formulary and inflated values from prior NICE technology appraisals.
- The base-case cost-effectiveness analysis applied list prices for G/P and all comparators. At a cost-effectiveness threshold of £20,000 per QALY gained, G/P was the cost-effective treatment in 13 of the 26 subgroups. In 12 of these subgroups G/P was associated with the lowest total costs, with G/P being dominant in 4 of these. As a confidential pricing agreement with CMU for G/P is currently under negotiation and several comparators have discounted pricing agreements, the prices used in the base-case, and the resulting ICERs, are not a realistic representation of the cost-effectiveness of G/P.
- In a pricing scenario analysis using the proposed confidential pricing agreement with CMU for G/P and OBV/PTV/RTV ± DSV [redacted]
- The key driver of the model was the SVR rate for G/P or comparator therapies in all but 1 subgroup. In this subgroup, health-state utility values were found to have the greatest impact on the results. A scenario analysis using health state utility values based on baseline EQ-5D observations from all Phase III G/P clinical trials and list prices for G/P and comparators demonstrated similar conclusions to the base-case.
- In summary, the economic evaluation presents a robust evaluation closely aligned to that of TA430. The pricing scenario analysis, which is more representative of the true price of G/P if it were used in clinical practice, finds G/P to represent a cost-effective treatment option across all 26 patient subgroups.

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify cost-effectiveness studies of DAAs for the treatment of HCV published since 2016. This review aimed to update the cost-effectiveness SLR conducted as part of the NICE appraisal of SOF/VEL (TA430).

The SLR identified 9 cost-effectiveness studies, none of which evaluated the cost-effectiveness of G/P. Details of these studies are provided in Appendix G.

B.3.2 *Economic analysis*

As noted above, no existing cost-effectiveness studies of G/P for the treatment of HCV were identified. As such, a de novo analysis was required for this submission. The studies of comparator therapies identified by the SLR were used to help guide the development of model structure and selection of inputs. In particular, three previous cost-effectiveness models with a UK perspective are referenced frequently throughout this section; a short description of each is included below:

- Wright et al. (2006) presents a cost-effectiveness model with a UK perspective, using data from the UK trial on mild HCV and an observational study of patients with more severe liver disease.[94]
- Shepherd et al. (2007) presents a cost-effectiveness model built by the Southampton Health Technology Assessments Centre to assess the cost-effectiveness of treatment strategies for adults with mild CHC in a UK setting.[95]
- Hartwell et al. (2011)[17] reviewed two economic models submitted by manufacturers to NICE (the models submitted by Roche and Schering-Plough for TA200[96]) and presented an independent economic analysis based on an adaptation of the model presented in Shepherd et al. (2007).[95]

B.3.2.1 Patient population

The population investigated in the economic model was adults with CHC. Patient subgroups presented in the model are defined by HCV genotype, treatment history, and fibrosis status, as summarised in Table 56 below. Treatment-experienced in the model is defined as meaning the patient has not adequately responded to prior IFN/RBV-based treatment with or without SOF, in line with the clinical trial programme of G/P (see Section B.2).

Base-case analyses for IFN-ineligible versus IFN-eligible patients are only presented for GT2 TN patients. Although some NICE guidance in other genotypes does specify IFN-eligibility, there is a greater unmet need for IFN-free treatment options for patients infected with GT2 compared to other genotypes, because GT2 is the genotype in which the SOF/VEL recommendation is restricted on the basis of IFN-eligibility. Therefore, GT2 is the genotype for which the question of IFN-eligibility remains a key consideration. The treatment and patient characteristics and costs are the same for the GT2 IFN-eligible versus the IFN-ineligible populations; the only difference is the comparators included in the analysis. The clinical trials for G/P did not stratify patients by IFN-eligibility.

This gives rise to a total of 26 subgroups (Table 56) explored in the explored in the economic analysis, which reflect the factors by which treatment decisions are stratified in clinical practice. Results for GT1 patients have not been further subdivided by subtype (1a and 1b). This is

because patients with GT1a and GT1b are treated similarly with G/P, and the difference in response between GT1a and GT1b is small and is unlikely to be a major issue from a clinical perspective and hence is unlikely to impact the results of economic analysis. This assumption therefore represents a pragmatic approach, and is one that has been previously considered acceptable by Evidence Review Groups (ERGs) as part of NICE appraisals in this indication.[97] This assumption is also in line with anticipated licence for G/P.

Table 56: Model populations and genotypes

GT	TN		TE[a]	
	NC[b]	CC[c]	NC[b]	CC[c]
1	X	X	X	X
2[d]	IFN-eligible: X IFN-ineligible: X	IFN-eligible: X IFN-ineligible: X	X	X
3	X	X	X	X
4	X	X	X	X
5	X	X	X	X
6	X	X	X	X

[a]Treatment-experience is defined as meaning the patient's hepatitis C has not adequately responded to IFN-based treatment; [b]METAVIR score F0–F3; [b]METAVIR score F4; [d]For GT2 TN patients, the only difference between the IFN-eligible and IFN-ineligible populations is the comparators considered. All other aspects are the same.
Abbreviations: CC, compensated cirrhosis; GT, genotype; IFN, interferon; NC, non-cirrhotic

Beyond the 26 subgroups described above, no further subgroups were explored in the economic analysis. The rationale for this is discussed in detail in Section B.1.1 in reference to the decision problem.

B.3.2.2 Model structure

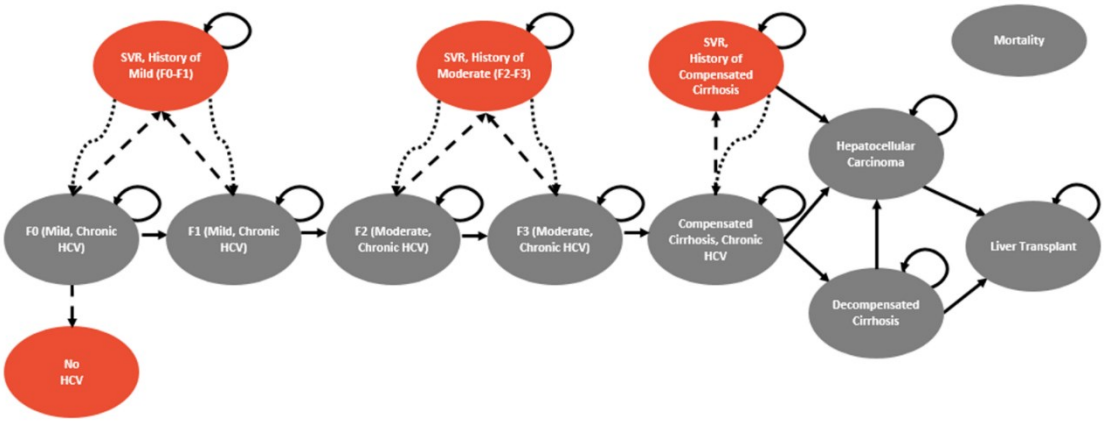
A cohort Markov state-transition model was built based on previously published models of the natural history of HCV infection.[17, 98, 99] This includes a model previously developed by AbbVie for OBV/PTV/RTV with or without DSV (TA365), which was assessed by NICE and received a positive recommendation.[99, 100]

The first phase of the model ('treatment phase') relates to the initial antiviral treatment period, which applies data from the clinical trials to estimate the proportion of patients who achieve SVR. When running the model to generate results for CC patients, 100% of the patients entering the 'treatment' phase of the model are assumed to have CC. When running the model to generate results for NC patients, patients are stratified by fibrosis severity (F0– F3) as they enter the 'treatment' phase of the model. Distinct SVR rates are applied to NC patients compared to CC patients (see Section B.3.3.2). No analyses were run using patients entering the first phase of the model in the DCC health state, as G/P is not licensed for use in this population.

Patients then move into the 'post-treatment' natural disease progression phase of the model. This phase of the model captures long-term outcomes over the remaining life of the patient and is depicted in Figure 1. Patients enter the relevant Markov health states of this phase of the model based on the proportion of patients that have achieved SVR. Those patients that achieve SVR enter recovered health states defined by their fibrosis history (SVR, history of mild [F0–F1] fibrosis; SVR, history of moderate [F2–F3] fibrosis; SVR, history of CC [F4]); patients that do not achieve SVR remain in the grey health states in Figure 15 and progress to more severe disease health states (DCC, HCC, and liver transplant [LT]).

Overall, the model therefore comprises the two key aspects of CHC: a treatment phase in which the efficacy of active treatments is captured in terms of achieving SVR; and a natural history phase that simulates the lifetime disease progression of patients with HCV following treatment with antiviral therapy depending on the outcome of the treatment phase.

Figure 15: Post-treatment, natural disease progression phase schematic



Note: Health states are depicted by ellipses; arrows represent permissible transitions between health states while loops represent no transition. Hashed arrows depict the possibility of achieving SVR. Dotted arrows depict a potential reinfection. Death is possible from any health state. Liver-related death is possible from DCC, HCC, and LT.
Abbreviations: DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C Virus; LT, liver transplant; SVR, sustained virologic response

B.3.2.2.1 Treatment phase

Patients are initiated on treatment in the first year/cycle of the model. Given the short durations of HCV treatments (8–16 weeks for G/P), all direct treatment-related outcomes and effects occur within the first year of the model. In line with previous HCV models, the model assumes that patients do not progress or die during the treatment period.[100, 101] With successful treatment, patients achieve SVR. Patients who do not achieve SVR are at risk of progressive liver disease, and are assumed to face the same risks of disease progression as untreated patients,[94] as described for the natural history phase in Section B.3.2.2.2. It is assumed that patients with DCC do not receive treatment (G/P is not licensed for the treatment of DCC).

B.3.2.2.2 Natural history phase

In the phase of the Markov state-transition model describing natural disease progression, each cycle represents one year. This part of the model includes a half-cycle correction, to adjust for the fact that patients would not only transition at the start or end of a given cycle.

The model structure is aligned with the clinical pathway of care for CHC. The model is based on a disease pathway of health states indicating progressive liver disease: four mild/moderate fibrosis states of increasing METAVIR scores, CC, DCC, HCC, LT and death (Figure 15). This structure is consistent with the core model structure that has been used across all submissions to NICE for HCV therapies, many of which have informed subsequent NICE recommendations.

CHC is a slowly progressing disease; the mean time to cirrhosis is estimated at 20 years, after which patients then advance to ESLD.[10] As disease progresses over this long time period, patients may die from non-liver related causes, and previous models have shown that the cost-effectiveness of treatment strategies is affected by initial fibrosis stage.[98] Therefore in the model

developed for this submission, patients are stratified by disease severity classified by METAVIR score as described by the health states in Figure 15. Previous economic models in NICE submissions (TA364 and TA413) have taken this approach[101, 102] and this is consistent with published literature.[98]

Patients progress through CHC states towards CC. A proportion of CC patients are then modelled to progress to DCC and HCC; a proportion of patients with DCC progresses to HCC.[103, 104] Although DCC can present simultaneously in multiple forms in any individual patient, DCC is modelled as a single health state, which is aligned with previously published models.[17, 98, 99, 105] HCC is modelled as two separate states for HCC (first year) and HCC (subsequent years) to allow for different inputs across the two different states. However, in all analyses the inputs across these two states are the same, and therefore there is effectively a single HCC state. A proportion of patients with DCC is modelled to receive a LT. Patients with HCC may also receive LTs. LT is modelled as two separate health states for LT (first year) and LT (subsequent years).

Throughout the model, patients are subject to a background risk of mortality equal to that of the general population. General mortality can occur from any Markov model health state. Additionally, patients in states representing more advanced liver disease, namely DCC, HCC or LT states, are at risk of liver-related death and therefore subject to increased risk of mortality; these states are commonly accepted as distinct stages of progressive liver disease and carry excess mortality risks.[17, 95, 106, 107]

B.3.2.2.3 Effects of SVR and assumptions about recovered states

Given the low probability of spontaneous clearance of HCV infection, it is assumed that spontaneous remission is not possible for patients with CHC, so the transition probability from F0 to the “no HCV” health state in Figure 15 is zero. Therefore, the only health states in the model representing recovery from CHC are the SVR states, into which patients enter with successful treatment as part of the ‘treatment phase’ of the model. SVR is assumed to be a permanent condition with no spontaneous reactivation of disease.

As there is robust clinical data demonstrating that SVR suspends the progression of liver fibrosis,[108-111] patients who achieve SVR are not assumed to progress to more severe liver disease. The exception to this is those patients with a history of CC. Whereas clinical evidence shows that patients who achieve SVR with a history of mild or moderate fibrosis have the same mortality risk and risk of developing HCC as the general population,[112, 113] patients who achieve SVR with a history of CC still face a risk of developing HCC even after achieving SVR.[112-117] Therefore, the model stratifies patients who achieve SVR by fibrosis severity (mild [F0-F1], moderate [F2-F3], CC [F4]), which is consistent with previously published models and accounts for differential risks faced by patients with different disease histories.[17, 98] As per Figure 15, patients who achieve SVR with a history of CC can transition to the HCC state.

Patients who do not achieve SVR are at risk of progressive liver disease, and are assumed to face the same risks of disease progression through the pathway described in Section B.3.2.2.2 as untreated patients.[94] Subsequent therapies (re-treatment due to treatment failure) are not included in the model. It is acknowledged that in clinical practice, patients who do not achieve SVR (due to lack of response or discontinuation due to AEs) may receive further lines of treatment; however, this re-treatment pathway is not well-defined, so the assumptions required to model re-treatment would add uncertainty to the model and its outcomes. Given this uncertainty, and the high success rates of treatment, and hence the low proportion of patients that experience treatment failure, omission of re-treatment is considered a reasonable simplification of the model.

Furthermore, this is a simplifying assumption that is consistent with previous modelling approaches that have been presented to NICE.[1, 100, 101]

B.3.2.2.4 Re-infection and onward transmission

Neither re-infection nor onward transmission is included in the model.

Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, with that risk being a function of the number of infectious individuals in the population.[118] Inclusion of onward transmission would likely result in a lower ICER for all active treatments, particularly those that are most effective, by capturing an aspect of the societal benefit of treatment in reducing onward transmission. In contrast, incorporating re-infection would likely result in a higher ICER for active treatments. Following re-infection, patients whose disease progression was previously halted by achieving SVR would advance to more severe liver disease states, which are associated with higher costs (see Table 82 in Section B.3.5.2), without the possibility of returning to an SVR state because subsequent therapies are not modelled.

Given that onward transmission could not be incorporated into the current modelling framework and that onward transmission and re-infection have contrasting impacts on cost-effectiveness, the approach was taken to exclude re-infection and onward transmission from the model. This is in line with previous conclusions by NICE that without a model that incorporates both re-infection and transmission, cost-effectiveness results excluding reinfection and transmission are acceptable for decision making.[97] Madin-Warburton et al. (2016) recently showed that there is a net positive impact on cost-effectiveness in a dynamic transmission model for treatment of HCV infection of incorporating both re-infection and onward transmission.[119] Therefore, the Markov model presented here may represent a conservative approach that under-estimates the cost-effectiveness of active treatments including G/P.

B.3.2.2.5 Key features of the analysis

There have been six NICE TAs in the past two years for DAA HCV therapies. The most recent such appraisal is that of SOF/VEL (TA430). This appraisal is also the most relevant, as it the only other appraisal to consider a pan-genotypic DAA. Therefore, in the interests of brevity and clarity, comparisons between the model presented in this submission and recent NICE TAs is limited to comparison with TA430.[1] Table 57 list the key features of the economic analysis, with comparison to TA430 (all key features are aligned). Sources of costs and utilities are compared to TA430 in later sections (Section B.3.4 and Section B.3.5).

Table 57: Key features of the analysis and comparison to TA430

Factor	TA430[1]	Current appraisal		
		Chosen values	Justification	Reference
Time horizon	Lifetime (until patients reach 100 years of age)	Lifetime (70 years after starting age)	The model time horizon is a lifetime horizon, which is appropriate for evaluating chronic HCV, where outcomes, including early mortality, are distributed over decades after the treatment decision has been made. The current model time horizon is consistent with previous models in NICE submissions.	Hartwell et al. (2011)[17]

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 annual basis	Annual	An annual cycle length is consistent with other previous models in NICE submissions.	Hartwell et al. (2011)[17]
Half-cycle correction	Applied from year 3 onwards (yearly transitions)	Half-cycle correction included	Patients transition between health states throughout the cycle, and not only at the start and end of each cycle. This feature is consistent with previous models in NICE submissions.	Hartwell et al. (2011)[17]
Were health effects measured in QALYs; if not, what was used?	QALYs	QALYs	The model is consistent with previous models in NICE submissions, and aligned with NICE methods guide.	Hartwell et al. (2011) and NICE (2013)[17, 120]
Discount rate for benefits and costs	3.5% for utilities and costs	3.5% for utilities and costs	The model is consistent with previous models in NICE submissions, and aligned with NICE methods guide.	Hartwell et al. (2011) and NICE (2013)[17, 120]
Perspective	NHS and PSS	NHS and PSS	The model is consistent with previous models in NICE submissions, and aligned with NICE methods guide.	Hartwell et al. (2011) and NICE (2013)[17, 120]

Abbreviations: HCV, hepatitis C virus; NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years

B.3.2.3 Intervention technology and comparators

The intervention considered in the model is G/P. G/P is awaiting marketing authorisation from the EMA, but the anticipated licensed dose is 300 mg/120 mg OD, with recommended treatment durations dependent on treatment experience and cirrhosis status as described in Table 58.

Table 58: Treatment duration for anticipated licence (not yet confirmed)

Patient population	NC	CC
TN	8 weeks for all genotypes	12 weeks for all genotypes
TE, previously treated with: • Peg-IFN + RBV • SOF + peg-IFN + RBV • SOF + RBV	GT1,2, 4–6: 8 weeks GT3: 16 weeks	GT1, 2, 4–6: 12 weeks GT3: 16 weeks

Abbreviations: CC, compensated cirrhosis; GT, genotype; NC, non-cirrhotic; peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve

Relevant comparator treatments were considered for each patient subgroup defined by genotype, cirrhosis status and prior treatment experience. Comparators were determined based on consideration of NICE-approved treatments for CHC, expert advice from English clinicians,

and the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1),[2] which represent current clinical practice, as outlined in Section B.1.4.

As described in Section B.3.2.1, for GT2 comparators were also defined specifically for subgroups of IFN-eligible and IFN-ineligible patients.

All treatment regimens were included as per their marketing authorisations and licensed doses, and as recommended by NICE. Comparators are described by genotype in Table 59. No treatment continuation rules are considered for G/P or any relevant comparators. Although NICE guidance recommends SOF + DCV for GT3 NC patients with significant fibrosis only, a pragmatic approach was taken to include this treatment as a comparator for all GT3 NC patients.

Table 59: Comparator treatments

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	CC	NC	CC
1	• SOF/VEL (12) • EBR/GZR[a] (12) • SOF/LDV (8) • OBV/PTV/RTV + DSV (12), 1a: + RBV • Best supportive care (watchful waiting)	• SOF/VEL (12) • EBR/GZR[a] (12) • SOF/LDV (12) • OBV/PTV/RTV + DSV (12), 1a: (24) + RBV[b] • Best supportive care (watchful waiting)	• SOF/VEL (12) • EBR/GZR[a] (12) • SOF/LDV (12) • OBV/PTV/RTV + DSV (12), 1a: + RBV • Best supportive care (watchful waiting)	• SOF/VEL (12) • EBR/GZR[a] (12) • SOF/LDV (12) • OBV/PTV/RTV + DSV (12), 1a: (24) + RBV[b] • Best supportive care (watchful waiting)
2	**Comparators for IFN-eligible patients:** • Peg-IFN + RBV (24) • Best supportive care (watchful waiting) **Comparators for IFN-ineligible patients:** • SOF/VEL (12) • SOF + RBV (12) • Best supportive care (watchful waiting)	**Comparators for IFN-eligible patients:** • SOF/VEL (12) • Best supportive care (watchful waiting) **Comparators for IFN-ineligible patients:** • SOF/VEL (12) • SOF + RBV (12) • Best supportive care (watchful waiting)	• SOF/VEL (12) • SOF + RBV (12) • Best supportive care (watchful waiting)	• SOF/VEL (12) • SOF + RBV (12) • Best supportive care (watchful waiting)
3	• SOF/VEL (12)	• SOF/VEL (12)	• SOF/VEL (12)	• SOF/VEL (12)

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	CC	NC	CC
	• SOF + DCV (12) • Best supportive care (watchful waiting)	• SOF + DCV + RBV (24) • SOF + peg-IFN + RBV (12) • SOF + RBV (24) • Best supportive care (watchful waiting)	• SOF + DCV (12) • SOF + peg-IFN + RBV (12) • Best supportive care (watchful waiting)	• SOF + DCV + RBV (24) • SOF + peg-IFN + RBV (12) • SOF + RBV (24) • Best supportive care (watchful waiting)
4	• SOF/VEL (12) • EBR/GZR[a] (12) • OBV/PTV/RTV + RBV (12) • Best supportive care (watchful waiting)	• SOF/VEL (12) • EBR/GZR[a] (12) • SOF/LDV (12) • OBV/PTV/RTV + RBV (12)[b] • Best supportive care (watchful waiting)	• SOF/VEL (12) • EBR/GZR[a] (12) • SOF/LDV (12) • OBV/PTV/RTV + RBV (12) • Best supportive care (watchful waiting)	• SOF/VEL (12) • EBR/GZR[a] (12) • SOF/LDV (12) • OBV/PTV/RTV + RBV (12)[b] • Best supportive care (watchful waiting)
5 or 6	• SOF/VEL (12) • Best supportive care (watchful waiting)	• SOF/VEL (12) • SOF + peg-IFN + RBV (12) • Best supportive care (watchful waiting)	• SOF/VEL (12) • Best supportive care (watchful waiting)	• SOF/VEL (12) • SOF + peg-IFN + RBV (12) • Best supportive care (watchful waiting)

[a]For the sake of simplicity the model assumes all patients receive a 12 week treatment duration without RBV[b]TA365 for OBV/PTV/RTV ± DSV was published before the results from TURQUOISE-III and AGATE-I became available and the NICE recommendation therefore stipulates the use of OBV/PTV/RTV ± DSV with RBV for GT1b patients with CC, and OBV/PTV/RTV + RBV for GT4 CC patients for 24 weeks. Subsequently, TURQUOISE-III demonstrated the efficacy of treatment with OBV/PTV/RTV + DSV for 12 weeks without RBV in GT1b patients with CC,[27] and AGATE-I demonstrated the efficacy of OBV/PTV/RTV + RBV for 12 weeks in GT4 patients with CC.[28] The licence for OBV/PTV/RTV ± DSV now reflects this. Therefore OBV/PTV/RTV + DSV without RBV for 12 weeks is used as the comparator in the economic analysis of this submission for GT1b patients with CC, and OBV/PTV/RTV + RBV for 24 weeks is used for GT4 CC patients

Abbreviations: CC, compensated cirrhosis; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; Peg-IFN, pegylated-IFN; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

B.3.3 *Clinical parameters and variables*

Key clinical data are listed in Table 60 and described further in the following subsections.

Table 60: Key clinical data

Characteristics	Data	Sources
Patient characteristics	• Age and gender distribution by treatment history at model entry • Fibrosis distribution at baseline	Adelphi Patient Chart Tracking Study UK (2017) and Harris et al. (1999)[31, 121] (Section B.3.3.1)
Treatment characteristics	• SVR rates • Treatment-related AEs • Treatment duration	Clinical trials (Section B.3.3.2)
HRQoL	Health state utilities and treatment-related quality of life (on-treatment utility reduction)	Clinical trial data and publications (Section B.3.4.1)

Abbreviations: AEs, adverse events; HRQoL, health-related quality of life; SVR, sustained virologic response

B.3.3.1 Patient characteristics

For the modelled cohorts, baseline characteristics relating to age, gender, genotype distribution and fibrosis distribution, by treatment experience status, were sourced from the Adelphi Chart Tracking Study, which represents market research performed by Adelphi Research UK amongst 75 specialist healthcare professionals in the UK. This study therefore reports relevant characteristics for the UK population of patients with CHC.

Modelling patient age enables relevant age-specific all-cause mortality rates (from the Office for National Statistics [2013–2015] National Life Tables for England) to be applied to patients as they progress through the model (see Table 232 in Appendix Section L.1.1).[122] Table 61 tabulates patient demographics (age and gender) in the base-case. These are different for TN and TE patients, and are independent of genotype and severity of liver disease. Base-case model results are presented in Section B.3.7 separately for NC patients (F0–F3) and CC patients (F4). The patient distribution between each METAVIR score (F0–F3) upon entry to the model for the analysis of NC patients is described in Table 62. For results for CC patients , 100% of patients are assumed to have CC at model entry. For GT1 patients, 68.1% are assumed to be GT1a, based on Harris et al. (1999), a study of the prevalence of GT1 sub-types in England and Wales.[121]

Unlike this model, TA430 specified a base-case age of 40 years for TN patients, and assumed that the population entering the model comprised 61% men and 39% females.[1] The reference for the gender distribution used in TA430 was Wright et al. (2006);[94] the input used in this model was chosen because it is more recent. Additionally, the model in TA430 did not have a fibrosis distribution as there were only two health states for patients with METAVIR scores of F0–F4: non-cirrhotic (F0 – F3) and compensated cirrhosis (F4).[1]

Table 61: Base-case patient demographics

Variable	Base-case value	Sources
TN		
Age (years)	43.0	Adelphi Research UK (2017)[31]
Male (%)	66.0%	
TE		
Age (years)	45.0	Adelphi Research UK (2017)[31]
Male (%)	71.0%	

Abbreviations: TE, treatment-experienced; TN, treatment-naïve

Table 62: Base-case patient distribution by METAVIR score for results for NC patients

Variable	Base-case value	Sources
TN		
F0	35.9%	Adelphi Research UK (2017)[31]
F1	45.7%	
F2	14.7%	
F3	3.8%	
TE		
F0	32.1%	Adelphi Research UK (2017)[31]
F1	33.6%	
F2	23.2%	
F3	11.1%	

Abbreviations: NC, non-cirrhotic; TE, treatment-experienced; TN, treatment-naïve

B.3.3.2 Treatment characteristics

Some simplifying assumptions are made for treatment regimens with different treatment recommendations for GT1a versus GT1b patients, patients with baseline HCV RNA levels over a specific threshold, and patients with specific NS5A polymorphisms.

For the purposes of calculating treatment costs for OBV/PTV/RTV + DSV, GT1a CC patients are assumed to have a treatment duration of 24 weeks with RBV, whereas GT1b CC patients are assumed to have a treatment duration of 12 weeks without RBV. However, a single SVR rate is applied to all GT1 TN CC patients, which is a weighted average of SVR rates from GT1a and GT1b patients receiving these regimens, respectively; a single SVR rate is also applied to all GT1 TE CC patients, again a weighted average of the SVR rates from GT1a and GT1b patients. As described in Section B.3.2.1, the difference in response between GT1a- and GT1b-infected patients is expected to be small and is unlikely to be a major issue from a clinical perspective, so it is reasonable to assume that GT1a and GT1b respond similarly to treatment.[97] For treatment with EBR/GZR, all GT1 and GT4 patients are assumed to receive 12 weeks of treatment without RBV, regardless of baseline HCV RNA levels (GT1 and GT4) or the presence of NS5A polymorphisms (GT1). This is a conservative assumption as it underestimates the cost of EBR/GZR in patients with specific baseline HCV RNA levels and/or NS5A polymorphisms that would in practice require longer treatment duration of 16 weeks with RBV.

Details of the trials providing inputs for G/P in the model are provided in Section B.2.3. Details of the trials providing the clinical inputs for comparator therapies are presented in Table 63.

Table 63: Trial sources for economic inputs for G/P comparators

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Primary study reference; *Secondary study reference(s)*
OBV (25 MG) / PTV (150 MG) / RTV (100 MG) OD + DSV (250 MG) BD						
3	AGATE-I	Randomised, open-label trial	Patients with CHC GT4 whose treatment status was not reported and had CC	OBV/PTV/RTV + RBV		Asselah 2016[28] and CSR for AGATE-I (AbbVie data on File)[123]
4	PEARL-I	Randomised, open-label study	Patients with CHC GT1b/4 who were treatment naive and TE and were NC or had CC	OBV/PTV/RTV + DSV		Hézode 2015b[124] and CSR for PEARL-I (AbbVie Data on File)[125]
5	PEARL-II	Randomised, open-label study	Patients with CHC GT1b who were TE and NC	OBV/PTV/RTV + DSV	OBV/PTV/RTV + DSV + RBV	Andreone 2014[126] and CSR for PEARL-II (AbbVie Data on File)[127]
6	PEARL-III	Randomised, double blind study	Patients with CHC GT1b who were TN and NC	OBV/PTV/RTV + DSV + RBV	OBV/PTV/RTV + DSV + Placebo RBV	Ferenci 2014[128] and updated CSR for PEARL-III (AbbVie Data on File)[129]
7	PEARL-IV	Randomised, double blind study	Patients with CHC GT1a who were TN and NC	OBV/PTV/RTV + DSV + RBV	OBV/PTV/RTV + DSV +Placebo RBV	Ferenci 2014[128] and updated CSR for PEARL-IV (AbbVie Data on File)[130]
8	TURQUOISE-II	Randomised, open-label study	Patients with CHC GT1 whose TN or TE status was not reported and had CC	OBV/PTV/RTV + DSV+ RBV	OBV/PTV/RTV + DSV + RBV	Poordad 2014[131] and CSR for TURQUOISE-II (AbbVie Data on File)[132]
9	TURQUOISE-III	Single-arm, open-label study	Patients with CHC GT1b who were TN and TE and had CC	OBV/PTV/RTV + DSV		Feld 2016[27] and CSR for TURQUOISE-III (AbbVie Data on File)[133]
11	SAPPHIRE-I	Randomised, double blind study	Patients with CHC GT1 who were TN and NC	OBV/PTV/RTV + DSV + RBV	Placebo followed by OBV/PTV/RTV + DSV + RBV	Feld 2014[134] and updated CSR for SAPPHIRE-I (AbbVie Data on File)[135]
12	SAPPHIRE-II	Randomised, double blind study	Patients with CHC GT1 who were TE and NC	OBV/PTV/RTV + DSV + RBV	Placebo followed by OBV/PTV/RTV + DSV + RBV	Zeuzem 2014b[136] and CSR for SAPPHIRE-II (AbbVie Data on File)[137]

EBR (50 MG) / GZR (100 MG) OD						
17	C-EDGE TE	Randomised, open-label study	Patients with CHC GT1/4/6 who were TE and were with or without cirrhosis	EBR/GZR ± RBV		Kwo 2017[138] and US PI[139]
20	C-EDGE TN	Phase II, randomised clinical trial	Patients with CHC GT1/4/6 who were TN	EBR/GZR	Placebo for 12 weeks, followed by the intervention	Zeuzem 2015[84] and US PI[139]
SOF (400 MG) / LDV (90 MG) OD						
23	ION-1	Randomised, open-label study	Patients with CHC GT1 who were TN and were with or without cirrhosis	SOF/LDV	SOF/LDV + RBV	Afdhal 2014b[140]
24	ION-2	Randomised, open-label study	Patients with CHC GT1 who were TE and were with or without cirrhosis	SOF/LDV	SOF/LDV + RBV	Afdhal 2014a[141]
25	ION-3	Randomised, open-label study	Patients with CHC GT1 who were TN and NC	SOF/LDV ± RBV	SOF/LDV	Kowdley 2014a[142]
26	Study 1119	Phase II, non-randomised, open-label study	Patients with CHC GT4/5 who were treatment naive and TE and were with or without cirrhosis	SOF/LDV		Abergel 2016[143]
SOF (400 MG) / VEL (100 MG) OD						
29	ASTRAL-1	Randomised, double blind study	Patients with CHC GT1/2/4/5/6 who were TN and TE and were with or without cirrhosis	SOF/VEL for 12 weeks	Placebo	Feld 2015[144]
30	ASTRAL-2	Randomised, open-label study	Patients with CHC GT2 who were TN and TE and were with or without cirrhosis	SOF/VEL fixed dose combination for 12 weeks	SOF + RBV for 12 weeks	Foster 2015b[145]
31	ASTRAL-3	Randomised, open-label study	Patients with CHC GT3 who were TN and TE and were with or without cirrhosis	SOF/VEL 12 weeks	SOF + RBV for 24 weeks	Foster 2015b[145]

N/A	POLARIS-3	Randomised, open-label study	Patients with CHC GT3 who were TN and TE and CC	SOF/VEL	SOF/VEL/VOX	Jacobson 2017[146] and Foster 2016[147]
SOF (400 MG) OD						
30	ASTRAL-2 - see details above					Foster 2015b[145] and TA430[1]
31	ASTRAL-3 - see details above					Foster 2015b[145] and TA430[1]
36	BOSON	Randomised, open-label study	Patients with CHC GT2/3 who were TN and TE and had CC	SOF + RBV ± IFN		Foster 2015a[148]
40	VALENCE	Randomised, double blind study	Patients with CHC GT2/3 who were treatment naive and TE and were with or without cirrhosis	SOF		Zeuzem 2014a[149] and Sovaldi Summary of Product Characteristics[150]
41	FUSION	Randomised, double blind study	Patients with CHC GT3 who were TE and were with or without cirrhosis	SOF + RBV	Placebo	Jacobson 2013,[151] Stepanova 2014[152] and Sovaldi Summary of Product Characteristics[150]
42	POSITRON	Randomised, double blind study	Patients with CHC GT2/3 who were IFN intolerant or ineligible and were with or without cirrhosis	SOF + RBV	Placebo	Jacobson 2013[151] and Stepanova 2014[152]
43	NEUTRINO	Single-arm, open-label study	Patients with CHC GT1/4/5/6 who were TN and were with or without cirrhosis	SOF + IFN + RBV		Lawitz 2013a,[153] Stepanova 2014[152] and Sovaldi Summary of Product Characteristics[150]
44	FISSION	Randomised, open-label study	Patients with CHC GT2/3 who were TN and had no hepatic decompensation	SOF + RBV	IFN + RBV	Lawitz 2013a,[154] Stepanova 2014[152] and Sovaldi Summary of Product Characteristics[150]
SOF (400 MG) / DCV (60 MG) OD						
47	ALLY3	Non-randomised, open-label study	Patients with CHC GT3 who were TN and TE and had no decompensated liver disease	SOF/DCV		Nelson 2015[155]

49	AI444040	Randomised, open-label study	Patients with CHC GT1/2/3 who were TN and were NC	SOF/DCV ± RBV		Sulkowski 2014[156]
N/A	ENDURANCE 3, see Section B.2.3					
PEG-IFN (180 µG WEEKLY)						
44	FISSION - see details above					
N/A	Treatment-related change in health utility was sourced from TA252[157]					

Abbreviations: BD, twice-daily; CC, compensated cirrhosis; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; GZR, grazoprevir; IFN, interferon; NC, non-cirrhotic; OBV, ombitasvir; OD, once-daily; PTV, paritaprevir; peg-IFN, pegylated IFN; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir; VOX, voxilaprevir; WTP, willingness-to-pay

B.3.3.2.1 SVR rates

SVR rates from relevant clinical trials for each treatment directly determine transition probabilities of patients moving from their baseline health state (mild or moderate fibrosis, or CC) into the recovered health state following successful treatment. In the absence of successful treatment, patients either remain in their respective health state or they progress to more severe stages of liver disease.

The clinical data used for SVR rates corresponds to SVR12, defined as HCV RNA <LLOQ at 12 weeks after the end of treatment, and based on the ITT population for each trial. There are currently a limited number of head-to-head trials for G/P and comparator treatments, and the available evidence is insufficient to build a robust network of G/P with relevant comparator therapies (see Section B.2.10.). In addition, study populations across the available head-to-head trials are heterogeneous (e.g. different genotypes and treatment histories), which would further compromise the validity and reliability of the analytic results. In the two most recent NICE submissions for HCV DAA therapies (TA413 and TA430), the development of a robust NMA suitable for use in an economic analysis was not possible due the available data.[1, 101] A matching-adjusted indirect comparison to SOF/VEL was also not deemed feasible as detailed in Section B.2.10.

Therefore, observed SVR12 rates from AbbVie trials and comparator trials were used directly in the model to determine the probability of patients achieving SVR following treatment. G/P trials were selected for inclusion in the economic model based on alignment with the anticipated licence, and data from registrational trials were used preferentially.

SVRs were determined separately for TN (Table 65) and TE (Table 66) patients, and within each of these subgroups the SVR rate is determined by fibrosis severity (NC [F0–F3] and CC [F4]). In the vast majority of cases, available clinical data did not distinguish between mild and moderate fibrosis in terms of SVR rates and hence the single available NC SVR rate was assumed to apply for patients in either the mild or moderate fibrosis health states. In the limited number of cases where granularity of clinical data provided, SVR rates separately for patients with mild fibrosis and for patients with moderate fibrosis, these individual SVR rates were applied in the model. The only instance of this is for SOF/LDV in GT1 TN patients.

Exhaustive lists of SVR rates used in the model are presented in Table 65 and Table 66. For comparator interventions that were also included in the model submitted in TA430,[1] the same sources for SVR rates were used for this model and the TA430 model, with the exceptions described in Table 64. Please note that Table 64 is not an exhaustive list of all SVR rate inputs – it details only those areas where there are differences between the SVR rate source used in TA430 and in this submission. In general, discrepancies are due to the fact this submission used recent sources that had not yet been published when TA430 was submitted. For best supportive care (no treatment), the SVR rate is assumed to be 0%.

Table 64: Differences in model inputs for SVR rates between TA430 and this submission

Subgroup	Treatment	TA430 source[1]	Source used in this submission
GT1 (general)	TA430 used distinct SVR rates for GT1a and GT1b patients. As discussed in Section B.3.2.1, in this submission a single SVR rate is used for all GT1 patients in line with the ERG's conclusion in the appraisal of TA430: the difference in response between GT1a and GT1b is small and is unlikely to be a major issue from a clinical perspective.[97]		

GT1 TN NC	OBV/PTV/RTV + DSV ± RBV	PEARL-III and PEARL IV	Weighted average of GT1a data from PEARL-IV and SAPPHIRE-I (pooled) and GT1b data from PEARL-III
GT1 TE NC	OBV/PTV/RTV + DSV ± RBV	PEARL-II	Weighted average of GT1a data from SAPPHIRE-II and GT1b data from PEARL-II
GT1 TE CC	OBV/PTV/RTV + DSV ± RBV	TURQUOISE-II	Weighted average of GT1a data from TURQUOISE-II and GT1b data from TURQUOISE-III
GT2 TN and TE, NC and CC	SOF + RBV	ASTRAL-2	Pooled data from FISSION (TN), FUSION (TE), VALENCE and ASTRAL-2
GT2 TN CC	Peg-IFN + RBV	ITC using ASTRAL-2 (SOF/VEL versus SOF + RBV) and FISSION (peg-IFN + RBV versus SOF + RBV) for SVR12 rates	This submission uses data from FISSION only for SVR12 rates, as an ITC was not feasible
GT3 TN and TE CC	SOF + DCV ± RBV	ALLY-3 (data for SOF + DCV 12 weeks)	Pooled data from VALENCE and ASTRAL-3 for TN, A1444040 for TE
GT3 TN and TE, CC	SOF + RBV	ASTRAL-3	Pooled data from ASTRAL-3 and VALENCE
GT3 TE CC	SOF/VEL	ASTRAL-3	Pooled data from ASTRAL-3 and POLARIS-3
GT4 TN and TE, CC	OBV/PTV/RTV + RBV	PEARL-I	AGATE-I

Abbreviations: AE, adverse event; CC, compensated cirrhosis; DSV, dasabuvir; ERG, Evidence Review Group; GT, genotype; IFN, interferon; ITC, indirect treatment comparison; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; Peg-IFN, pegylated IFN; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

Table 65: SVR inputs for TN patients using clinical trial data

Patient population (TN)	Regimen	F0–F3 (NC)			F4 (CC)		
		Treatment duration (weeks)	SVR12 % (n/N)	Reference	Treatment duration (weeks)	SVR12 % (n/N)	Reference
GT1	G/P	8	[redacted]	ENDURANCE-1 ITT-PS TN population[46]	12	[redacted]	EXPEDITION-1 ITT TN population[57]
	OBV/PTV/RTV + DSV ± RBV	1a: 12 (+ RBV) 1b: 12	[redacted]	GT1a: Pooled data from PEARL-IV (CSR)[130] and SAPPHIRE-I (CSR)[135] GT1b: PEARL-III (CSR)[129]	1a: 24 (+ RBV) 1b: 12	96.4%[a]	GT1a and G1b: TURQUOISE-II[131]
	EBR/GZR	12[b]	93.2%[c]	C-EDGE TN (US PI)[139]	12[b]	95.9%[c]	C-EDGE TN (US PI)[139]
	SOF/LDV	8	F0–F1: 95.2% (80/84) F2–F3: 94.4% (68/72)	ION-3[142]	12	94.1% (32/34)	ION-1[140]
	SOF/VEL	12	98.4% (251/255)[d]	ASTRAL-1[144]	12	98.6% (72/73)[d]	ASTRAL-1[144]
GT2	G/P	8	[redacted]	SURVEYOR-II, pooled data from ITT TN population in Parts 2 and 4[64]	12	[redacted]	EXPEDITION-1 ITT TN population[57]
	SOF/VEL	12	99.0% (99/100)[d]	ASTRAL-2[145]	12	100.0% (15/15)[d]	ASTRAL-2[145]
	SOF + RBV	12	96.3% (180/187)	Pooled data from FISSION (Sovaldi SmPC),[150] VALENCE[149] and ASTRAL-2 (TA430)[1]	12	89.7% (26/29)	Pooled data from FISSION (Sovaldi SmPC),[150] VALENCE[149] and ASTRAL-2 (TA430)[1]
	Peg-IFN + RBV	24	81.5% (44/54)	FISSION (Sovaldi SmPC)[150]	Not a comparator		
GT3	G/P	8	94.9% (149/157)	ENDURANCE-3 ITT population[52, 88]	12	[redacted]	SURVEYOR-II, pooled data from ITT TN population in Parts 2 and 3[64]

Patient population (TN)	Regimen	F0–F3 (NC)			F4 (CC)		
		Treatment duration (weeks)	SVR12 % (n/N)	Reference	Treatment duration (weeks)	SVR12 % (n/N)	Reference
	SOF/VEL	12	98.2% (160/163)	ASTRAL-3[145]	12	96.7% (116/120)	Pooled data from ASTRAL-3[145] and POLARIS-3[146, 147]
	SOF + DCV ± RBV	12	96.8% (184/190)	Pooled data from ENDURANCE-3 ITT population[52, 88] and ALLY-3[155]	24 (+ RBV)	100% (5/5)	A1444040[156]
	SOF + RBV	Not a comparator			24	77.6% (45/58)	Pooled data from VALENCE (Sovaldi SmPC)[150] and ASTRAL-3 (TA430)[1]
	SOF + peg-IFN + RBV	Not a comparator			12	91.3% (21/23)	BOSON[148]
GT4	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TN population[64]	12	[redacted]	EXPEDITION-1 ITT TN population[57]
	OBV/PTV/RTV + RBV	12	100.0% (42/42)[a, e]	PEARL-I[124]	12	96.7% (29/30)[a]	AGATE-I[28]
	EBR/GZR	12[b]	100.0% (16.71/16.71)[f]	C-EDGE TN (Zeuzem et al. [215] and US PI)[84, 139]	12[b]	100.0% (1.29/1.29)[f]	C-EDGE TN (Zeuzem et al. [215] and US PI)[84, 139]
	SOF/LDV	Not a comparator			12	100.0% (1/1)	Study 1119[158]
	SOF/VEL	12	100.0% (89/89)[d]	ASTRAL-1[144]	12	100.0% (27/27)[d]	ASTRAL-1[144]
GT5	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TN population[64]	12	[redacted]	EXPEDITION- ITT TN population[57]
	SOF/VEL	12	96.6% (28/29)[d]	ASTRAL-1[144]	12	100.0% (5/5)[d]	ASTRAL-1[144]
	SOF + peg-IFN + RBV	Not a comparator			12	50% (1/2)[g]	NEUTRINO (Sovaldi SmPC)[150]

Patient population (TN)	Regimen	F0–F3 (NC)			F4 (CC)		
		Treatment duration (weeks)	SVR12 % (n/N)	Reference	Treatment duration (weeks)	SVR12 % (n/N)	Reference
GT6	G/P	8	[redacted]	SURVEYOR-II, Part 4 ITT TN population[64]	12	[redacted]	EXPEDITION-1 ITT TN population[57]
	SOF/VEL	12	100.0% (35/35)[d]	ASTRAL-1[144]	12	100.0% (6/6)[d]	ASTRAL-1[144]
	SOF + peg-IFN + RBV	Not a comparator			12	50% (1/2)[g]	NEUTRINO (Sovaldi SmPC)[150]

[a]SVR in GT1 patients is calculated using a weighted average of SVRs in GT1a and GT1b patients, and n/N is not reported; [b]For simplicity, the model assumes all patients receive EBR/GZR for 12 weeks; [c]SVR in GT1 patients is calculated using a weighted average of SVRs in GT1a and GT1b patients, and n/N is not reported; [d]Data available included the following: (i) SVR data stratified by cirrhosis status for TN and TE patients combined and (ii) overall SVR data stratified by TN and TE patients. The former were used and it was assumed that TN=TE; [e]'RBV-eligible' patients; [f]The number of GT4 NC and CC patients was calculated, assuming the percentage of CC patients was the same between GT4 and GT6 patients. The percentage of CC patients among GT4 and GT6 patients was calculated from the percentage of patients among the GT1, GT4 and GT6 patient population available in the trial publication[84] and the percentage of patients among the GT1 population available in the US package insert.[139] The calculated n/N is reported to 2 decimal places; [g]Data for overall GT4, GT5 and GT6 population.

Abbreviations: CC, compensated cirrhosis; CSR, clinical study report; DAA, direct-acting antiviral; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ITT, intention-to-treat; ITT-PS, ITT mono-infected GT1 DAA-naïve; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PI package insert; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SmPC, summary of product characteristics; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

Table 66: SVR Inputs for TE patients using clinical trial data

Patient population (TE)	Regimen	F0–F3 (NC)			F4 (CC)		
		Treatment duration (weeks)	SVR12 % (n/N)	Reference	Treatment duration (weeks)	SVR12 % (n/N)	Reference
GT1	G/P	8	[redacted]	ENDURANCE-1 ITT-PS TE population[46]	12	[redacted]	EXPEDITION-1 ITT TE population[57]
	OBV/PTV/RTV + DSV ± RBV	1a: 12 (+ RBV) 1b: 12	97.4%[a,b]	GT1a: SAPPHIRE-II[136] GT1b: PEARL-II[126]	1a: 24 (+ RBV) 1b: 12	98.5%[a,b]	GT1a: TURQUOISE-II[131] GT1b: TURQUOISE-III[27]
	EBR/GZR	12[c]	93.4%[d]	C-EDGE TE (US PI)[139]	12[c]	93.2%[d]	C-EDGE TE (US PI)[139]
	SOF/LDV	12	95.4% (83/87)	ION-2[141]	12	86.4% (19/22)	ION-2[141]
	SOF/VEL	12	98.4% (251/255)[e]	ASTRAL-1[144]	12	98.6% (72/73)[e]	ASTRAL-1[144]
GT2	G/P	8	[redacted]	SURVEYOR-II, pooled data from ITT TE population in Part 2 and Part 4[64]	12	[redacted]	EXPEDITION-1 ITT TE population[57]
	SOF/VEL	12	100.0% (15/15)[e]	ASTRAL-2[145]	12	100.0% (4/4)[e]	ASTRAL-2[145]
	SOF + RBV	12	88.5% (69/78)	Pooled data from FUSION (Sovaldi SmPC),[150] VALENCE (Sovaldi SmPC)[150] and ASTRAL-2 (TA43)[1]	12	77.3%	Pooled data from FUSION (Sovaldi SmPC),[150] VALENCE (Sovaldi SmPC)[150] and ASTRAL-2 (TA43)[1]
GT3	G/P	16	95.5% (21/22)	SURVEYOR-II, Part 3 ITT TE population[64, 65]	16	[redacted]	SURVEYOR-II, pooled data from ITT TE population in Parts 2 and 3[64]
	SOF/VEL	12	91.2% (31/34)	ASTRAL-3[145]	12	89.9% (62/69)	Pooled data from ASTRAL-3[145] and POLARIS-3[146, 147]
	SOF + DCV ± RBV	12	94.1% (32/34)	ALLY-3[155]	24 (+ RBV)	100% (5/5)[f]	A1444040[156]

Patient population (TE)	Regimen	F0–F3 (NC)			F4 (CC)		
		Treatment duration (weeks)	SVR12 % (n/N)	Reference	Treatment duration (weeks)	SVR12 % (n/N)	Reference
	SOF + RBV	Not a comparator			24	59.0% (49/83)	Pooled data from VALENCE (Sovaldi SmPC)[150] and ASTRAL-3 (TA430)[1]
	SOF + peg-IFN + RBV	Not a comparator			12	85.7% (30/35)	BOSON[148]
GT4	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TE population[64]	12	[redacted]	EXPEDITION-1 ITT TE population[57]
	OBV/PTV/RTV + RBV	12	100.0% (49/49)[a, b]	PEARL-I[124]	12	98.2% (N=29)[a, b, h]	AGATE-I[28]
	EBR/GZR	12[c]	100.0% (3.00/3.00)[i]	C-EDGE TE (Kwo et al. [2016] and US PI)[138, 139]	12[c]	66.7% (4.00/6.00)[i]	C-EDGE TE[138, 139]
	SOF/LDV	12	84.6% (11/13)	Study 1119[158]	12	100.0% (9/9)	Study 1119[158]
	SOF/VEL	12	100.0% (89/89)[e]	ASTRAL-1[144]	12	100.0% (27/27)[e]	ASTRAL-1[144]
GT5	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TE population[64]	12	[redacted]	EXPEDITION-1 ITT TE population[57]
	SOF/VEL	12	100.0% (11/11)[e]	ASTRAL-1[144]	12	100.0% (11/11)[e]	ASTRAL-1[144]
	SOF + peg-IFN + RBV	Not a comparator			12	50% (1/2)[j]	NEUTRINO (Sovaldi SmPC)[150]
GT6	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TE population[64]	12	[redacted]	EXPEDITION-1 ITT TE population[57]
	SOF/VEL	12	100.0% (35/35)[e]	ASTRAL-1[144]	12	100.0% (6/6)[e]	ASTRAL-1[144]
	SOF + peg-IFN + RBV	Not a comparator			12	50% (1/2)[j]	NEUTRINO (Sovaldi SmPC)[150]

Patient population (TE)	Regimen	F0–F3 (NC)			F4 (CC)		
		Treatment duration (weeks)	SVR12 % (n/N)	Reference	Treatment duration (weeks)	SVR12 % (n/N)	Reference

[a]SVR in GT1 patients is calculated using a weighted average of SVRs in GT1a and GT1b patients, and n/N is not reported; [b]Data are weighted among null response, partial response and prior relapse patients; [c]For simplicity, the model assumes all patients receive EBR/GZR for 12 weeks; [d]SVR in GT1 patients is calculated using a weighted average of SVRs in GT1a and GT1b patients, and n/N is not reported; [e]Data available included the following: (i) SVR data stratified by cirrhosis status for TN and TE patients combined and (ii) overall SVR data stratified by TN and TE patients. The former were used and it was assumed that TN=TE, except in GT5 TE where the latter is used. This is done because the SVR rate in this subgroup is 100% and using the data in (i) would imply an SVR rate below 100% (whereas one F0–F3 TN patient did not achieve SVR); [f]Assumed to be the same as for TN; [g]There were low numbers of GT4, GT5 and GT6 TE patients recruited, so pooled results from GT4-, GT5- and GT6-infected patients were used; [h]In GT4 F4 where SVR≠100%, only the consolidated 'N' is reported; [i]The number of GT4 NC and CC patients was calculated, assuming the percentage of CC patients was the same between GT4 and GT6 patients. The percentage of CC patients among GT4 and GT6 patients was calculated from the percentage of patients among the GT1, GT4 and GT6 patient population available in the trial publication[138] and the percentage of patients among the GT1 population available in the US package insert;[139] [j]Assumed to be the same as TN (data for overall GT4, GT5 and GT6 population), same assumption as TA430[1]

Abbreviations: CC, compensated cirrhosis; CSR, clinical study report; DCV, daclatasvir; DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ITT, intention-to-treat; ITT-PS, ITT mono-infected GT1 DAA-naïve; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

B.3.3.2.2 Treatment-related AEs

Inputs for AE rates are described in Table 68 for TN patients and Table 69 for TE patients. The AE rates are used to calculate costs. Five AEs were included in the model: anaemia, depression, rash, Grade 3/4 neutropaenia and Grade 3/4 thrombocytopaenia. In the model submitted for TA430, which is relevant for comparison as SOF/VEL is also a pan-genotypic treatment, other AEs including nausea, vomiting, diarrhoea and pruritus were included.[1] In this model, the effect of AEs on HRQoL is incorporated using treatment-related change in health utility (see Section B.3.4.5.3), which is based on PROs. Therefore, all treatment-related effects (and as such, the impact of all treatment-related AEs) are captured, not just the effects of AEs listed in Table 68 and Table 69. Nausea, vomiting, diarrhoea and pruritus were excluded from explicit consideration in the model because the costs associated with these AEs are very small and thus have minimal impact on the cost-effectiveness estimates. The AEs that are included in the model have larger associated costs (see Section B.3.5.3) that have the potential to impact on cost-effectiveness estimates.

The sources used to extract AE data are described in Table 65 for TN patients and Table 66 for TE patients. AE rates were not reported separately in some references for NC patients and CC patients; in these cases, the same AE rates are applied for these two patient populations. For best supportive care (no treatment), the AE rate is assumed to be 0% for all AEs. Table 67 describes difference in data sources between TA430 and this submission. As for SVR rates, in general more recent sources were used in this submission.

Table 67: Differences in model inputs for AE rates between TA430 and this submission

Subgroup	Treatment	TA430 source[1]	Source used in this submission
GT1	OBV/PTV/RTV + DSV ± RBV	Assumed 0% for all AEs	As per Table 68 and Table 69
GT2 TN and TE, NC and CC	SOF + RBV	VALENCE and FISSION (TN) or FUSION (TE)	Pooled data from FISSION (TN), FUSION (TE), VALENCE and ASTRAL-2
GT3 TN and TE, NC and CC	SOF/VEL	ASTRAL-3	Pooled data from ASTRAL-3 and POLARIS-3
GT3 TN and TE, NC and CC	SOF + DCV ± RBV	ALLY3 (data from SOF + DCV 12 weeks)	Pooled data from ENDURANCE-3 and ALLY-3 for TN and A1444040 for TE
GT3 TN and TE, CC	SOF + RBV	VALENCE	Pooled data from ASTRAL-3 and VALENCE
GT3 TN and TE CC	SOF + peg-IFN + RBV	Assumed equal to NEUTRINO	BOSON
GT4 TN and TE, CC	OBV/PTV/RTV + RBV	PEARL-I	AGATE-I

Abbreviations: AE, adverse event; CC, compensated cirrhosis; DSV, dasabuvir; ERG, Evidence Review Group; GT, genotype; IFN, interferon; ITC, indirect treatment comparison; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; Peg-IFN, pegylated IFN; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir.

Table 68: Inputs for AEs in TN patients using clinical trial data

Patient population (TN)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropoenia	Grade 3/4 thrombocy-topaenia	Reference
GT1	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ENDURANCE-1[46]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	OBV/PTV/RTV + DSV ± RBV	NC	3.84%	7.88%	0.00%	0.15%	0.15%	Pooled data from SAPPHIRE-I[134] and PEARL-IV[128]; weighted average with PEARL-III[128]
		CC	7.13%	10.96%	4.75%	1.19%	1.06%	TURQUOISE-II[131]
	EBR/GZR	NC	2.85%	0.00%	0.00%	0.32%	0.00%	C-EDGE TN[84]
		CC	2.85%	0.00%	0.00%	0.32%	0.00%	
	SOF/LDV	NC	0.93%	1.40%	0.00%	0.00%	0.00%	ION-3[142]
		CC	0.47%	4.88%	0.00%	0.47%	0.23%	ION-1[140]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
GT2	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.00%	0.00%	ASTRAL-2[145]
		CC	0.00%	0.00%	0.00%	0.00%	0.00%	
	SOF + RBV	NC	4.24%	4.87%	3.18%	0.21%	0.00%	Pooled data from FISSION,[151] VALENCE[149] and ASTRAL-2[151]
		CC	4.24%	4.87%	3.18%	0.21%	0.00%	
	Peg-IFN + RBV	NC	11.52%	17.70%	13.99%	14.81%	7.41%	FISSION[154]

Patient population (TN)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropoenia	Grade 3/4 thrombocy-topaenia	Reference
GT3	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ENDURANCE-3 [52, 88]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 3 [64]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.26%	0.52%	Pooled data from ASTRAL-3 [145] and POLARIS-3 [146, 147]
		CC	0.00%	0.00%	0.00%	0.26%	0.52%	
	SOF + DCV ± RBV	NC	0.00%	0.75%	0.00%	0.00%	0.75%	Pooled data from ENDURANCE-3 [52, 88] and ALLY-3 [155]
		CC	7.14%	0.00%	14.29%	0.00%	0.00%	A1444040 [156]
	SOF + RBV	CC	0.00%	0.00%	0.19%	0.00%	0.76%	Pooled data from VALENCE [149] and ASTRAL-3 [145]
	SOF + peg-IFN + RBV	CC	0.00%	19.80%	0.51%	15.74%	4.57%	BOSON [148]
GT4	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4 [64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1 [57]
	OBV/PTV/RTV + RBV	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	PEARL-I (CSR) [125]
		CC[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AGATE-I (CSR) [123]
	EBR/GZR	NC	2.85%	0.00%	0.00%	0.32%	0.00%	C-EDGE TN [84]
		CC	2.85%	0.00%	0.00%	0.32%	0.00%	
	SOF/LDV	CC	0.00%	0.00%	0.00%	0.00%	4.55%	Study 1119 [158]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1 [144]

Patient population (TN)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropoenia	Grade 3/4 thrombocy-topaenia	Reference
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
GT5	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	CC	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[153]
GT6	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	CC	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[153]

Note: For published references, if AEs were not reported (for example because only AEs affecting >5% of patients were reported), these were assumed to have a frequency of 0.
Abbreviations: AEs, adverse events; CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TN, treatment-naïve; VEL, velpatasvir

Table 69: Inputs for AEs in TE patients using clinical trial data

Patient population (TE)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropoenia	Grade 3/4 thrombocy-topaenia	Reference
GT1	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ENDURANCE-1[46]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	OBV/PTV/RTV + DSV ± RBV	NC	3.67%	6.30%	0.00%	0.00%	0.00%	Weighted average of PEARL-II[126] and SAPPHIRE-II[136]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TURQUOISE-III (Feld et al. [2016][27] and CSR[133])
	EBR/GZR	NC	0.00%	0.00%	0.00%	0.00%	0.00%	C-EDGE TE[138]
		CC	0.00%	0.00%	0.00%	0.00%	0.00%	
	SOF/LDV	NC	0.00%	1.83%	0.00%	0.00%	0.92%	ION-2[141]
		CC	0.00%	1.83%	0.00%	0.00%	0.92%	
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
GT2	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.00%	0.00%	ASTRAL-2[145]
		CC	0.00%	0.00%	0.00%	0.00%	0.00%	
	SOF + RBV	NC	3.45%	2.19%	2.19%	0.63%	0.63%	Pooled data from FUSION,[151]
		CC	3.45%	2.19%	2.19%	0.63%	0.63%	

Patient population (TE)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropoenia	Grade 3/4 thrombocy-topaenia	Reference
								VALENCE[149] and ASTRAL-2[151]
GT3	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 3[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 3[64]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.26%	0.52%	Pooled data from ASTRAL-3[145] and POLARIS-3[146, 147]
		CC	0.00%	0.00%	0.00%	0.26%	0.52%	
	SOF + DCV ± RBV	NC	0.00%	0.00%	0.00%	0.00%	1.32%	ALLY-3[155]
		CC	7.14%	0.00%	14.29%	0.00%	0.00%	A1444040[156]
	SOF + RBV	CC	0.00%	0.00%	0.19%	0.00%	0.76%	Pooled data from VALENCE[149]and ASTRAL-3[145]
	SOF + peg-IFN + RBV	CC	0.00%	19.80%	0.51%	15.74%	4.57%	BOSON[148]
GT4	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	OBV/PTV/RTV + RBV	NC[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	PEARL-I(CSR)[125]
		CC[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AGATE-I (CSR)[123]
	EBR/GZR	NC	0.00%	0.00%	0.00%	0.00%	0.00%	C-EDGE TE[138]
		CC	0.00%	0.00%	0.00%	0.00%	0.00%	
	SOF/LDV	NC	0.00%	0.00%	0.00%	0.00%	4.55%	Study 1119[158]

Patient population (TE)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropoenia	Grade 3/4 thrombocy-topaenia	Reference
		CC	0.00%	0.00%	0.00%	0.00%	4.55%	
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
GT5	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	CC	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[153]
GT6	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	CC	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[153]

Note: For published references, if AEs were not reported (for example because only AEs affecting >5% of patients were reported), these were assumed to have a frequency of 0.
Abbreviations: AEs, adverse events; CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; VEL, velpatasvir

B.3.3.2.3 Treatment duration

The cost per course of a therapy was calculated as the sum product of the daily cost of each component of the regimen and the mean duration of treatment in days. The identified literature was inconsistent and in some cases poorly transparent in terms of the reporting of average treatment durations in the relevant clinical trials. Therefore, average treatment durations were derived based on a calculation that aimed to take account of treatment durations for patients who completed treatment early and those who discontinued treatment before study completion.

For this calculation, the numbers of patients who 1) received at least one dose of the study drug, 2) completed the study, and 3) discontinued the study early, were retrieved from published clinical trials. This information was extracted from the same published sources as for SVR rates and AE rates (see Table 65 and Table 66). For patients who discontinued early, it was assumed that discontinuation had occurred at the mid-point of trial duration.

Based on this, the following calculation was therefore used to provide an estimate of average treatment duration:

Equation 1: calculation of treatment duration

$$Average\ Treatment\ Duration = \left\{\frac{A}{A+B} \times Total\ Treatment\ Duration\right\} + \left\{\frac{B}{A+B} \times Total\ Treatment\ Duration \times 0.5\right\}$$

Where A is the number of patients who completed study and B is the number of patients who did not complete the study.

Table 70 and Table 71 summarise the expected treatment duration for each regimen resulting from this calculation. In TA430, the percentage of patients who discontinued treatment for any reason as reported by the relevant trials was used to determine treatment duration in the model.[1]

Table 70: Expected duration by patient subgroup and treatment regimen: TN patients

Patients (TN)	Regimen	Cirrhosis status	Expected duration (days)	Reference
GT1	G/P	NC	[redacted]	ENDURANCE-1[46]
		CC	[redacted]	EXPEDITION-1[57]
	OBV/PTV/RTV + DSV ± RBV[a,]	NC	83.5 (RBV 56.7)	Pooled data from SAPPHIRE-I[134] and PEARL-IV[128]; weighted average with PEARL-III[128]
		CC	138.2 (RBV 111.4)	TURQUOISE-II[131]
	EBR/GZR	NC	83.6	C-EDGE TN[84]
		CC	83.6	
	SOF/LDV	NC	56.0	ION-3[142]
		CC	83.3	ION-1[140]
	SOF/VEL	NC	83.9	ASTRAL-1[144]
		CC	83.9	
GT2	G/P	NC	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 4[64]
		CC	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	83.7	ASTRAL-2[145]
		CC	83.7	
	SOF + RBV	NC	82.9 (RBV 82.9)	Pooled data from FISSION,[151] VALENCE[149] and ASTRAL-2[151]
		CC	82.9 (RBV 82.9)	
	Peg-IFN + RBV	NC	149.3 (RBV 149.3)	FISSION[154]
GT3	G/P	NC	[redacted]	ENDURANCE-3[52]
		CC	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 3[64]
	SOF/VEL	NC	83.6	Pooled data from ASTRAL-3[145] and POLARIS-3[146, 147]
		CC	83.6	
	SOF + DCV ± RBV	NC	83.7	Pooled data from ENDURANCE-3 ITT population[52, 88] and ALLY-3[155]
		CC	156.0 (RBV 156.0)	A1444040[156]
	SOF + RBV	CC	164.0 (RBV 164.0)	Pooled data from VALENCE[149]and ASTRAL-3[145]
	SOF + peg-IFN + RBV	CC	83.1 for all components	BOSON[148]

Patients (TN)	Regimen	Cirrhosis status	Expected duration (days)	Reference
GT4	G/P	NC	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	EXPEDITION-1[57]
	OBV/PTV/RTV + RBV[b]	NC	84.0 (84.0)	PEARL-I[124]
		CC	82.6 (RBV 82.6)	AGATE-I[28]
	EBR/GZR	NC	83.6	C-EDGE TN[84]
		CC	83.6	
	SOF/LDV	CC	84.0	Study 1119[158]
	SOF/VEL	NC	83.9	ASTRAL-1[144]
		CC	83.9	
GT5	G/P	NC	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	83.9	ASTRAL-1[144]
		CC	83.9	
	SOF + peg-IFN + RBV	CC	83.1 for all components	NEUTRINO[153]
GT6	G/P	NC	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	83.9	ASTRAL-1[144]
		CC	83.9	
	SOF + peg-IFN + RBV	CC	83.1 for all components	NEUTRINO[153]

Note: For studies that presented the number of patients who discontinued and completed treatment for the study as a whole or with insufficient granularity to divide by cirrhosis status and treatment history, it was assumed that treatment duration was the same across these sub-populations.
[a]GT1a patients treated with OBV/PTV/RTV + DSV were treated with RBV whereas GT1b patients were not treated with RBV. Thus there is a difference in the weighted duration for OBV/PTV/RTV + DSV and RBV;
Abbreviations: CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

Table 71: Expected duration by patient subgroup and treatment regimen: TE patients

Patients (TE)	Regimen	Cirrhosis status	Expected duration (days)	Reference
GT1	G/P	NC	[redacted]	ENDURANCE-1[46]
		CC	[redacted]	EXPEDITION-1[57]
	OBV/PTV/RTV + DSV ± RBV[a]	NC	83.5 (RBV 56.7)	Weighted average of SAPPHIRE-II[136] and PEARL-II[126]
		CC	138.2 (RBV 111.4)	Weighted average of TURQUOISE-II[131] and TURQUOISE-III[27]
	EBR/GZR	NC	83.6	C-EDGE TE[138]
		CC	83.6	
	SOF/LDV	NC	84.0	ION-2[141]
		CC	84.0	
	SOF/VEL	NC	83.9	ASTRAL-1[144]
		CC	83.9	
GT2	G/P	NC	[redacted]	SURVEYOR-II, pooled data from Part 2 and Part 4[64]
		CC	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	83.7	ASTRAL-2[145]
		CC	83.7	
	SOF + RBV	NC	83.7 (RBV 83.7)	Pooled data from FUSION,[151] VALENCE[149] and ASTRAL-2[151]
		CC	83.7 (RBV 83.7)	
GT3	G/P	NC	[redacted]	SURVEYOR-II Part 3[64]
		CC	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 3[64]
	SOF/VEL	NC	83.6	Pooled data from ASTRAL-3[145] and POLARIS-3[146, 147]
		CC	83.6	
	SOF + DCV ± RBV	NC	83.7	ALLY-3[155]
		CC	156.0 (RBV 156.0)	BOSON[148]
	SOF + RBV	CC	164.0 (RBV 164.0)	Pooled data from VALENCE[149]and ASTRAL-3[145]
	SOF + peg-IFN + RBV	CC	83.1 for all components	A1444040[156]
GT4	G/P	NC	[redacted]	SURVEYOR-II, Part 4 [64]
		CC	[redacted]	EXPEDITION-1[57]
		NC	84.0 (84.0)	PEARL-I[124]

Patients (TE)	Regimen	Cirrhosis status	Expected duration (days)	Reference
	OBV/PTV/RTV + RBV[b]	**CC**	82.6 (RBV 82.6)	AGATE-I[28]
	EBR/GZR	**NC**	83.6	C-EDGE TE[138]
		CC	83.6	
	SOF/LDV	**NC**	84.0	Study 1119[158]
		CC	84.0	
	SOF/VEL	**NC**	83.9	ASTRAL-1[144]
		CC	83.9	
GT5	**G/P**	**NC**	[redacted]	SURVEYOR-II, Part 4 [64]
		CC	[redacted]	EXPEDITION-1[57]
	SOF/VEL	**NC**	83.9	ASTRAL-1[144]
		CC	83.9	
	SOF + peg-IFN + RBV	**CC**	83.1 for all components	NEUTRINO[153]
GT6	**G/P**	**NC**	[redacted]	SURVEYOR-II, Part 4 [64]
		CC	[redacted]	EXPEDITION-1[57]
	SOF/VEL	**NC**	83.9	ASTRAL-1[144]
		CC	83.9	
	SOF + peg-IFN + RBV	**CC**	83.1 for all components	NEUTRINO[153]

Note: For studies that presented the number of patients who discontinued and completed treatment for the study as a whole or with insufficient granularity to divide by cirrhosis status and treatment history, it was assumed that treatment duration was the same across these sub-populations. [a]GT1a patients treated with OBV/PTV/RTV + DSV were treated with RBV whereas GT1b patients were not treated with RBV. Thus there is a difference in the weighted duration for OBV/PTV/RTV + DSV and RBV

Abbreviations: CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

B.3.3.3 Calculation of transition probabilities from the clinical data

SVR rates from the trials (ITT perspective) directly determine transition probabilities of patients moving from their baseline health state (mild or moderate fibrosis, or CC) into the recovered health state (retaining the memory about their stage of disease prior to SVR) following successful treatment (see Section B.3.3.2). Non-treatment specific transition probabilities (i.e. those determining the natural disease progression) were derived from the literature as summarised in Table 75. The sources are described in the sections that follow.

B.3.3.3.1 Fibrosis progression

Age-dependent fibrosis progression transition probabilities for GT1 were calculated using equations from Thein et al. (2008): a systematic review and meta-analysis that calculated stage-specific progression rates from a meta-regression analysis.[159] The transition rate equations published by Thein et al. (2008) incorporate the influence of the duration of HCV infection (in years), age at infection, sex (% male), genotype (% GT1), source of infection (such as intravenous drug use [IDU] or blood transfusion) and excessive alcohol consumption (defined as alcohol consumption of at least more than 20g/day in the 12 months prior to study entry).[159] These equations have been used by previous UK HTAs (TA253 and TA364) to obtain annual fibrosis stage specific transition rates.[102, 160]

Equations to estimate stage-specific progression rates from Thein et al. (2008) [159]

$$F0-F1\ transition\ rate = \exp(-\beta1 + \beta2 \times duration + \beta3 \times design + \beta4 \times male + \beta5 \times genotype)$$

$$F1-F2\ transition\ rate = \exp(-\beta1 - \beta2 \times duration + \beta3 \times excess\ alcohol)$$

$$F2-F3\ transition\ rate = \exp(-\beta1 + \beta2 \times age - \beta3 \times duration + \beta4 \times excess\ alcohol)$$

$$F3-F4\ transition\ rate = \exp(-\beta1 + \beta2 \times age - \beta3 \times duration + \beta4 \times injecting\ drug\ users + \beta5 \times blood\ transfusion + \beta6 \times genotype)$$

Notes: Duration of HCV infection and age at HCV acquisition in years; study design: cross-sectional/retrospective = 1; retrospective-prospective = 0; Other values range from 0 to 1.
Abbreviations: exp, exponential function

In line with TA364, the equations above were populated with the patient baseline characteristics used in the base-case for TA364 (Table 72) and the log-linear regression equation coefficients described in TA364 (Table 73) to calculate fibrosis stage-specific transition rates for GT1. The resulting transition rates were converted to transition probabilities for GT1 as described in Table 74.

Table 72: Patient baseline characteristics used in TA364[102]

Parameter	Mean	SE	Distribution	Source
Age (years)	50	0.2	NORMAL	HCV Research UK database, as reported by TA364[102]
Male proportion (%)	67	0.4	BETA	Hepatitis C in the UK 2014 report[161]
Duration (years)	16.93	3.53	BETA	Weighted average of all UK studies included in Thein et al. (2008)[159]
IDU proportion (%)	59.34	3.13	BETA	
Blood transfusion proportion (%)	26.85	2.85	BETA	
Excess alcohol proportion (%)	23.78	2.43	BETA	
Design	1	N/A	N/A	Assumption
Genotype	1	N/A	N/A	GT1 only

Abbreviations: GT, genotype; HCV, hepatitis C virus; IDU, injecting drug use; N/A, not applicable

Table 73: Log-linear regression equation coefficients used to derive age-dependent fibrosis stage-specific transition rates in TA364[102]

Transition	Coefficient	Mean	Standard error	Distribution
F0 to F1	Intercept (β1)	2.0124	0.664	NORMAL
	Duration (β2)	0.07589	0.011	NORMAL
	Design (β3)	0.3247	0.175	NORMAL
	Male (β4)	0.5063	0.478	NORMAL
	Genotype (β5)	0.4839	0.278	NORMAL
F1 to F2	Intercept (β1)	1.5387	0.818	NORMAL
	Duration (β2)	0.06146	0.014	NORMAL
	Excess alcohol (β3)	0.8001	0.391	NORMAL
F2 to F3	Intercept (β1)	1.6038	0.59	NORMAL
	Age (β2)	0.0172	0.012	NORMAL
	Duration (β3)	0.05939	0.01	NORMAL
	Excess alcohol (β4)	0.4539	0.28	NORMAL
F3 to F4	Intercept (β1)	2.2898	0.773	NORMAL
	Age (β2)	0.01689	0.015	NORMAL
	Duration (β3)	0.03694	0.013	NORMAL
	IDU (β4)	0.5963	0.316	NORMAL
	BT (β5)	1.1682	0.368	NORMAL
	Genotype (β6)	0.4652	0.291	NORMAL

Notes: Duration: Length of time from the presumed date of infection to the date of liver biopsy; Design: Value=0 if the study design is cross sectional; value=1 if the study design is retrospective-prospective; Male: Proportion of patients that are male; Genotype: Proportion of patients that are genotype 1; Excess alcohol: Defined as alcohol consumption of at least more than 20 g/day. Age: Age at date of infection; Proportion of patients that acknowledged IDU as the main risk factor for HCV progression; Proportion of patients that were newly diagnosed with CHC at blood donor screening.

Abbreviations: BT, blood transfusion; CHC, chronic hepatitis C; HCV, hepatitis C virus; IDU, injecting drug use

Table 74: Conversion of fibrosis stage-specific transition rates to transition probabilities

Transition	Rate	Transition probability
F0 to F1	0.117	0.110
F1 to F2	0.092	0.088
F2 to F3	0.194	0.176
F3 to F4	0.154	0.143

Transition probabilities were calculated according to the following formula: transition probability = 1 – exp (rate)

Genotype affects the rate of liver disease progression; for example, GT3-infection is associated with accelerated fibrosis progression and increased risk of cirrhosis and HCC.[162, 163] Kanwal et al. (2014) evaluated the clinical progression of over 100,000 US armed forces veterans over 10 years, and calculated adjusted hazard ratios for the incidence of cirrhosis and HCC for GT1, GT2, GT3 and GT4 infection.[163] Whilst this is a non-UK study, in a previous submission to NICE (TA430) the applicability of this study to a UK setting was accepted by clinical experts.[1] Therefore these hazard ratios have been used as 'GT-specific progression multipliers' applied to the transition probabilities for liver disease progression for GT1. In the absence of equivalent hazard ratios for GT5 and GT6, the GT4 hazard ratio was assumed to apply to GT5 and GT6. These hazard ratios are presented in Table 75.

Notably, TA430 did not distinguish between non-cirrhotic fibrosis health states, and transition probabilities from fibrosis to CC were calculated directly from Kanwal et al. (2014).[1, 163]

B.3.3.3.2 Non-fibrosis disease progression

Progression to HCC from the "SVR with a history of CC" state was sourced from Cardoso et al. (2010),[164] a French study analysing the incidence of liver-related complications in over 300 patients with severe fibrosis and cirrhosis. Progressions between CC, DCC and HCC were taken from Fattovich et al. (1997), a study of the incidence of liver-related complications in nearly 400 European cirrhotic patients.[103] The use of these two sources is aligned with Wright et al. (2006), Shepherd et al. (2007) and Hartwell et al. (2011), all of which present cost-effectiveness analyses of HCV therapies in the UK setting.[17, 94, 95] This is an area of deviation from TA430, which used Cardoso et al. (2010) for the transition probabilities for progressions between CC, DCC and HCC.[164] Previous economic models have used both sources for base-case values for NICE submissions, and it has been concluded that both estimates are generalisable to clinical practice and the true value lies somewhere between.[97]

Unlike TA430,[1] this model also applies a GT-specific progression multiplier to the transition from CC and DCC to HCC. Kanwal et al. (2014) calculated adjusted hazard ratios for the incidence of HCC for GT1, GT2, GT3 and GT4 infection, and these hazard ratios were therefore applied to the transition probabilities for transition from CC and DCC to HCC.[163] In the absence of equivalent hazard ratios for GT5 and GT6, the GT4 hazard ratio was assumed to apply to GT5 and GT6.

B.3.3.3.3 LT

Transition probabilities for transition from DCC to LT and HCC to LT were sourced from Siebert et al. (2003), a cost-effectiveness analysis of IFN/RBV regimens.[17, 165] This study took an estimate of the rate of liver transplantation for HCV in the US and revised this estimate down to 2%, assuming that the rate of transplantation would be lower in Europe (and the UK) compared to the US, and used this as the transition probability from DCC to LT.[165] This approach has been taken by previous UK cost-effectiveness models such as Wright et al. (2006), Shepherd et al.

(2007), Grieve et al. (2006) and Hartwell et al. (2011).[17, 94, 95, 107] In line with Wright et al. (2006) and the model developed by Schering-Plough scrutinised in Hartwell et al. (2011),[17, 94] this rate is applied to the transition to LT from HCC as well. TA430 also sourced the transition probability from DCC to liver transplant from Seibert and colleagues; the transition from HCC to liver transplant was not included in the model in TA430.[1, 166] The model in this submission allows liver transplantation for patients with HCC as this is in line with current UK clinical practice.[167]

B.3.3.3.4 Liver-related mortality

Transition probabilities for DCC and HCC to liver death were sourced from Fattovich et al. (1997), in line with the models presented by Wright et al. (2006), Shepherd et al. (2007) and Hartwell et al. (2011). [17, 94, 95] The same value was applied for HCC to liver death as for TA430.[1] For the transition from DCC to liver death, TA430 used a higher value sourced from early access programme (EAP) data from the EASL; however, the value used in this model is consistent with other models submitted recently to NICE such as TA413, TA365 and TA364.[1, 100-102, 168]

The value for the probability of death in the year following liver transplantation (LT – first year) was sourced from a survival analysis of UK LT registry data, which has been used in previously UK cost-effectiveness studies including Grieve et al. (2006), Shepherd et al. (2007), and Hartwell et al. (2011).[17, 95, 107] For the transition from LT (subsequent year) to liver death, the value was sourced from Bennett et al. (1997), a cost-effectiveness study of IFN-α 2b in patients with CHC,[169] in line with the models presented in Shepherd et al. (2007) and Hartwell et al. (2011).[17, 95] In TA430, a single transition probability for liver transplant to death was used from Bennett et al (1997),[169] which is higher than those used in this model. However, the value used in this model is consistent with other models submitted recently to NICE such as TA365 and TA364.[1, 100, 102, 168]

Table 75: Annual transition probabilities

Variable	Base-case value	Source	TA430 value and reference[1]
GT1 fibrosis progression			
F0-F1	0.110	Equations from Thein et al. (2008)[159] and patient characteristics from TA364[102]	Model did not distinguish between non-cirrhotic fibrosis health states
F1-F2	0.088		
F2-F3	0.176		
F3-CC	0.143		See section below
GT-specific fibrosis progression multipliers			
GT2	0.68	Kanwal et al. (2014)[163] (adjusted hazard ratio)	F3-CC genotype-specific transition probabilities were calculated from Kanwal et al. (2014)[163]; GT1 0.0213, GT2 0.0165, GT3 0.0296, GT4 0.0202, GT5 0.0202, GT6 0.0202
GT3[a]	1.30		
GT4	0.94		
GT5	0.94	Assume same as GT4	
GT6	0.94		
Non-fibrosis disease progression			
SVR, history of CC (F4) to HCC	0.012	Cardoso et al. (2010)[164]	Same value and reference
CC to DCC	0.039	Fattovich et al. (1997)[103]	0.0438 Cardoso et al. (2010)[164]

Variable	Base-case value	Source	TA430 value and reference[1]
CC to HCC; GT1	0.014		0.0631 Cardoso et al. (2010)[164]
DCC to HCC; GT1	0.014		0.0631 Cardoso et al. (2010)[164]
GT-specific non-fibrosis transition rate multipliers			
CC to HCC multiplier			
GT2	0.62	Kanwal et al. (2014)[163]	Not applied
GT3	1.44		
GT4	0.96		
GT5	0.96	Assumed same as GT4	
GT6	0.96		
DCC to HCC multiplier			
GT2	0.62	Assumed same as CC to HCC multiplier	Not applied
GT3	1.44		
GT4	0.96		
GT5	0.96		
GT6	0.96		
LT			
DCC to LT (first year)	0.020[b]	Siebert et al. (2003)[165]	0.022 Siebert et al. (2005)[166]
HCC to LT (first year)	0.020[b]		Transition not allowed in model
Liver-related mortality			
DCC to liver death	0.130	Fattovich et al. (1997)[103]	0.24 EAP data (EASL 2016)[168]
LT first year to liver death	0.150	Grieve et al. (2006)[107]	0.2100 Bennett et al (1997)[169]
LT subsequent year to liver death	0.057	Bennett et al. (1997)[169]	
HCC to liver death	0.430	Fattovich et al. (1997)[103]	Same value and reference
Spontaneous remission from F0	0.000	Assumption (see Section B.3.2.2.3)	Same assumption
Background age- and gender-adjusted probability of death	Variable	ONS (2016)[122]	Same value and reference

Variable	Base-case value	Source	TA430 value and reference[1]

[a]The inputs are based on Table 2 from Kanwal et al. (2014).[163] Note that there is a discrepancy in the publication for the GT3 fibrosis progression multiplier. In the introduction and the results section, the text mentions 1.31, but the results in Table 2 shows 1.30; [b]For the transition probability form DCC to LT, Siebert et al. (2003)[165] actually use 0.022; Shepherd et al. (2011), and Wright et al. (2006) and Hartwell et al. (2011) use 0.02, so the model presented here has aligned with these other UK models.[17, 94, 95]
Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; GT, genotype; HCC, hepatocellular carcinoma; LT, liver transplant; ONS, Office of National Statistics; SVR, sustained virologic response

The transition probabilities used in the base-case do not vary with age except for: the transition probability to death from all causes and the age-dependent fibrosis stage-specific transition rates.

B.3.4 *Measurement and valuation of health effects*

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

To take into account the effect of DAA therapy and to account for the impact of AEs associated with treatment on patients' HRQoL, patient utility is adjusted in the year of treatment by a treatment-related health utility change that reflects the impact of treatment on utility over the treatment period.

For G/P, these treatment-related changes in health utility were calculated using HRQoL data collected in the clinical trials. HRQoL data were collected in all trials for G/P listed in the clinical section (Section 7) except for the MAGELLAN trials. Treatment-related changes in health utility were calculated using data from treatment arms from with G/P treatment durations aligned with the anticipated licence. EQ-5D-3L data were gathered from Phase III trials (ENDURANCE-1, ENDURANCE-3 and EXPEDITION-1) EQ-5D-5L data from the Phase II SURVEYOR-II trial. PRO instruments were administered according to the schedule described in Table 76. For ENDURANCE-1, patients co-infected with HIV were excluded from the analysis in order to ensure any variance in HRQoL could be attributed solely to HCV and treatment with G/P.

Table 76: Administration of PRO instruments during clinical trials for G/P

Trial	Treatment period			Post-treatment period		
	Baseline	Week 4	EOT or D/C[c]	Week 4	Week 12	Week 24 or D/C[c]
ENDURANCE-1[a]	X		X		X	
ENDURANCE-3[a]	X	X	X		X	X
EXPEDITION-1[a]	X	X	X		X	X
SURVEYOR-II[b]	X		X	X		

[a]EQ-5D-3L; [b]EQ-5D-5L; [c]Patients who prematurely discontinued the treatment period should have returned to the site to complete premature discontinuation procedures. Similarly, patients who prematurely discontinued from the post-treatment period should have returned to the site to complete post-treatment discontinuation treatment procedures; [d]Not required for patients who were randomised to receive placebo in the double-blind treatment period.
Abbreviations: D/C, discontinuation; EOT, end of treatment; G/P glecaprevir/pibrentasvir; PRO, patient reported outcome; PT, post-treatment

PRO questionnaire results from each of these trials are reported in Appendix Section D.4 as EQ-5D index scores. Because the questionnaires were administered at baseline and at end of

treatment, this enables a change in treatment-related health utilities to be calculated. UK tariffs were applied to EQ-5D-3L data,[170] while the UK crosswalk value set was applied to EQ-5D-5L data to convert these to EQ-5D-3L scores.[171] UK tariffs and UK crosswalk values were applied to all EQ-5D score elicited from the entire patient sample, irrespective of their study location, in order to obtain utilities associated with G/P treatment as perceived by the UK general population. AbbVie has previously used this method in a prior technology appraisal presented to NICE (TA365).[100] It was assumed that treatment-related changes in health utility for G/P are independent of genotype, treatment history and fibrosis severity, and instead are determined by treatment duration. Therefore, for each G/P treatment duration the value represents a weighted average of all the trial arms for that particular treatment duration.

For comparator therapies, the treatment-related changes in health utility were derived from published literature, where available (the same sources as for SVR and AE rates, and treatment duration). The treatment-related change in health utility was calculated as the difference between the baseline utility of patients and the utility 12 weeks after the end of treatment. Where no data on treatment-related health utility existed, simplifying assumptions using available data were made, as described in detail in Section B.3.4.5.3.

B.3.4.2 Mapping

EQ-5D-3L or EQ-5D-5L data were reported directly in the Phase III and Phase II trials listed in Table 76. Therefore, no mapping was required in order to generate a treatment-specific change in health utility for G/P.

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

An SLR was conducted to identify HRQoL studies in patients with chronic HCV infection. This SLR was conducted as an update to the SLR for HRQoL conducted as part of the NICE appraisal of SOF/VEL (TA430). This SLR identified four new studies reporting EQ-5D scores for patients with HCV, as reported in Appendix H. However, none of the four studies provided utility values that were more appropriate to inform the economic analysis than the studies that have been used previously in prior appraisals of therapies for HCV.

B.3.4.4 Adverse reactions

IFN- and RBV-based antiviral treatments are associated with significant side-effects that negatively impact quality of life.[17] The introduction of IFN- and RBV-free regimens has improved the tolerability of antiviral treatments, although as with all pharmaceuticals there are side-effects associated with treatment. The impact of treatment-related AEs on patient HRQoL was implicitly captured in the model via the application of treatment-related change in health utility values (see Section B.3.4.5.3).

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

Health state utilities were applied from identified literature and are described in Section B.3.4.3. In addition to health state utilities, treatment-dependent changes in health utility were applied in order to take into account the potential impact of adverse effects of antiviral therapy on patients' HRQoL (see B.3.4.5.3). These treatment-related changes in health utility were applied during the treatment period.

B.3.4.5.1 Patient experience of health states in terms of HRQoL

CHC has been shown to result in lower HRQoL compared with the general population. The patient experience of HRQoL for the health states included in the model is as follows:

- *Early stages of liver disease: mild (F0–F1) and moderate (F2–F3) fibrosis and CC (F4).* Symptoms in people with CHC are typically mild and non-specific, and include fatigue, flu-like symptoms, anorexia, depression, sleep disturbance, cognitive impairment, right upper quadrant pain, itching and nausea.[17] Although at this stage of the disease patients do not experience liver-specific symptoms, the non-specific symptoms can cause a significant decrease in quality of life. Wright et al. (2006) found that disease symptoms tend to correlate with the degree of liver fibrosis, with a proportional impact on HRQoL as measured by EQ-5D.[94] Some patients may also experience extra-hepatic symptoms (renal, dermatologic, hematologic and rheumatologic) due to HCV elsewhere in the body.[10] Recently people with CHC have been shown to have impaired cognitive function and evidence of central nervous system involvement, even in patients with mild liver disease.[94] Social stigma associated with having CHC is also known to negatively impact patients' emotional status and, therefore, HRQoL, with stigma arising from a fear of transmission and perceived associations of HCV with HIV and AIDS, promiscuity, and substance abuse.[15] Finally, patients experience a decline in quality of life (QoL) with diagnosis of CHC itself.[172]
- *DCC.* This health state is associated with the development of a variety of liver-related complications, such as ascites, upper gastrointestinal bleeding secondary to varices or portal hypertensive gastropathy, and hepatic encephalopathy, all of which further negatively impact HRQoL.[10]
- *HCC.* Compared to patients with chronic liver disease, patients with HCC had worse physical well-being and overall HRQoL than patients with chronic liver disease, mainly in terms of pain, loss of appetite and weight, difficulties digesting food, and decreased ability to perform usual activities.[173]
- *LT.* Although liver transplantation increases HRQoL due to alleviation of liver-related symptoms and improvements in physical functioning, HRQoL remains significantly lower for patients post-transplant compared to the general population.[174]
- *SVR.* Following successful treatment, it has been shown that patients have significant improvements in HRQoL, for example due to symptom alleviation and improved emotional and psychological status.[94]

As described previously, side-effects of antiviral therapies can reduce HRQoL during the treatment period. The impact of treatment-related adverse events on patient HRQoL was implicitly captured in the model via the application of treatment-related change in health utility values (see Section B.3.4.5.3).

B.3.4.5.2 Summary of health state utility values

Health state utility values for the economic analysis were informed by the same published sources as have been used in prior appraisals of therapies for HCV. An updated SLR identified no new published literature providing utility values more appropriate than the literature sources that have been used previously.

Published literature was used in preference to the EQ-5D health state valuations from the G/P clinical trials. As described previously, the EQ-5D health state valuations were converted to a single preference based health utility index score using UK tariffs for the entire patient sample,

irrespective of their study location. However, as UK patients represented only a small percentage of the total enrolled patient sample, it was felt that these utilities would not be representative of the UK patients suffering with CHC and thus it was decided to use health state utilities identified from the literature. Furthermore, the trials for G/P did not enrol patients with DCC, HCC, or LTs. No health effects identified in the literature or clinical trials have been excluded from the analysis.

The utilities chosen for the current model are based on 1) the UK trial on mild HCV by Wright et al. (2006);[94] 2) the observational study of patients with more severe liver disease conducted alongside the UK trial on mild HCV by Wright et al. (2006);[94] and 3) a UK study of costs and outcomes following liver transplantation by Ratcliffe et al. (2002). These utility values are summarised in Table 77.[175] These data are appropriate to the NICE reference case for measuring and valuing health benefits as QoL measurements were undertaken using the EQ-5D.[120] The sources used are largely consistent with those used to define health state utilities in TA430, as detailed in Table 77.

A utility increment of 0.05 is assumed for achieving SVR for patients with mild and moderate fibrosis, and CC, and is assumed to occur in the second cycle of the model onwards. This utility gain was based on data collected in the UK trial on mild HCV by Wright et al. (2006) and used to calculate the health state utility value for SVR with a history of mild (F0–F1) or moderate (F2–F3) fibrosis by Wright et al. (2006); the +0.05 increment was applied to the health state utility value for SVR with a history of CC by Shepherd et al. (2007) and Hartwell et al. (2011), and by previous NICE TAs.[17, 94, 95, 100, 101]

Because the model presented in TA430 did not distinguish between non-cirrhotic health states, in TA430 a single health state utility value was applied to patients with F0–F3 fibrosis severities; however, this value was sourced from the same reference as the health state utilities used in this model.[1] The utilities for health states representing advanced liver disease are consistent between this model and TA430. [1] The SVR utility increment applied in this model is different from that in TA430; in TA430 an SVR utility increment of +0.04 from Vera-Llonche et al. [2013])[176] was applied.

In the model submitted in TA430, utilities were age-adjusted; age-adjustments are not applied in the base-case of this model. As noted in the committee assessment of TA430, age-based utility decrements had very little effect on the ICERs in TA430,[97] and therefore using base-case values that are not age-adjusted is a suitable approach.

Finally, a scenario analysis using health state utilities derived from G/P trials was also conducted to explore the impact of this altenative source of utility values on model results. It was considered more appropriate to use literature-derived health-state utility values in the base-case for consistency with previous appraisals in chronic HCV.

Table 77: Summary of health state utilities

Health state	Base-case value	Source	TA430 value and reference[1]
F0	0.77	Wright et al. (2006)[94]	0.750 Wright et al. (2006)[94]
F1	0.77		
F2	0.66		
F3	0.66		
CC	0.55		Same value and reference

Health state	Base-case value	Source	TA430 value and reference[1]
SVR, history of mild fibrosis (F0, F1)	0.82	+0.05 added to mild fibrosis health state; Wright et al. (2006)[94] and aligned with Shepherd et al. (2007) and Hartwell et al. (2011)[17, 95]	0.790 (calculated from SVR utility increment of +0.04 from Vera-Llonche et al. [2013])[176]
SVR, history of moderate fibrosis (F2, F3)	0.71	+0.05 added to moderate fibrosis health state[a]	
SVR, history of CC (F4)	0.60	+0.05 added to CC health state. Utility aligned with Shepherd et al. (2007) and Hartwell et al. (2011)[17, 95]	0.590 (calculated; ERG: 0.55)
DCC	0.45	Ratcliffe et al. (2002);[175] used in model by Wright et al. (2006)[94]	Same value and reference
HCC	0.45		
LT (first year)	0.45	Ratcliffe et al. (2002);[175] used in model by Wright et al. (2006)[94]	
LT (subsequent)	0.67	Ratcliffe et al. (2002);[175] used in model by Wright et al. (2006)[94]	

[a]This value (0.71) is consistent with previous appraisals using a +0.05 utility increment for achieving SVR (e.g. TA413 and TA365),[100, 101] however, Hartwell et al. (2011), Shepherd et al.(2007) and Wright et al (2006) (referenced in these appraisals) used a value of 0.72.[17, 94, 95] The value of 0.71 has been used here to prioritise consistency with previous appraisals.
Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; ERG, Evidence Review Group; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; SVR, sustained virologic response

B.3.4.5.3 Treatment-related change in health utility

Treatment-related health utility changes per the expected regimen duration were annualised (for example, a 12-week change would be reweighted by multiplying it by 12/52), and annualised treatment-related health utility changes (summarised in Table 78) were applied to baseline utilities from Wright et al. (2006)[94] in cycle 1 of the model, in which treatment is received. For best supportive care (no treatment), the treatment-related change in health utility is 0.

The methodology for calculating and applying treatment-related utilities is different from that of TA430.[1] In TA430 the manufacturer applied treatment-specific utility increments for DAA therapies because they are not associated with the AEs of IFN and RBV (which were comparators in the model in TA430) and improve QoL due to rapid early suppression of the virus. Utility decrements were applied for each AE. The approach taken in this model is simplifying, conservative and associated with reduced uncertainty, as a single utility change per treatment is applied for the duration of treatment. No utility decrements are applied for individual AEs as this may lead to double-counting, as the effect of treatment-related AEs on HRQoL would be captured in the treatment-related utility adjustment.

Table 78: Annualised treatment-related health utility changes by treatment and patient population

Regimen (duration in weeks) and patient population			Annualised change in treatment-related health utility	Reference
G/P (8)			[redacted]	Weighted average of TN NC populations from GT1 ENDURANCE-1 (HCV mono-infected patients only),[46] GT2 SURVEYOR-II pooled data from Part 2 and Part 4[64] and GT3 ENDURANCE-3[52]
G/P (12)			[redacted]	Weighted average of TN CC populations from GT1 EXPEDITION-1[57] and GT3 SURVEYOR-II, pooled data from Parts 2 and 3[64]
G/P (16)			[redacted]	Weighted average of TN CC populations from GT3 SURVEYOR-II, Parts 2 and 3[64]
OBV/PTV/RTV + DSV ± RBV	**GT1, TN**	**NC (12)**	[redacted]	Pooled data from SAPPHIRE-I (CSR)[135] and PEARL-IV (CSR)[130]; weighted average with PEARL-III (CSR)[129]
		CC (12 or 24)	[redacted]	TURQUOISE-II (CSR)[132]
	GT1, TE	**NC (12)**	[redacted]	Weighted average of SAPPHIRE-II (CSR)[137] and PEARL-II (CSR)[127]
		CC (12)	[redacted]	Weighted average of TURQOUISE-II (CSR)[132] and TURQOUISE-III (CSR)[133]
OBV/PTV/RTV ± RBV[b]	**GT4, TN**	**NC (12)**	[redacted]	PEARL-I (CSR)[125]
		CC (12)	[redacted]	AGATE-I (CSR)[123]
	GT4, TE	**NC (12)**	[redacted]	PEARL-I (CSR)[125]
		CC (12)	[redacted]	AGATE-I (CSR)[123]
EBR/GZR (12)[a]			0	C-EDGE TN and C-EDGE TE as reported in TA413[101]
SOF/LDV (12)			0	TA363[177]
SOF/VEL (12)[b]			0.007	Assumed same as G/P 12 weeks
SOF + DCV ± RBV (12)	**TN**	**NC**	-0.002	Average of ENDURANCE-3[52, 88] and ALLY-3[155]
		CC	-0.027	A1444040[156]
	TE	**NC**	-0.008	ALLY-3[155]
		CC	-0.027	A1444040[156]
SOF + peg-IFN + RBV (12)			-0.034	NEUTRINO[152]
SOF + RBV (12)	**GT2, TN**	**NC**	-0.001	FISSION[152]
		CC	-0.001	
	GT2, TE	**NC**	-0.006	Average of FUSION[152] and FISSION[152]
		CC	-0.006	
SOF + RBV (24)	**GT3, TN**	**CC**	-0.024	POSITRON[152]
	GT3, TE	**CC**	-0.024	

Peg-IFN + RBV (24)	**GT2, TN**	**NC**	-0.050	TA252[157]

[a]EQ-5D data was extracted from TA413 for C-EDGE TN.[101] It was assumed conservatively that the on-treatment change in health utility also applies to TE patients; [b]The ASTRAL trials did not collect EQ-5D data. The same treatment-related change in health utility as G/P (12 weeks) was assumed.
Abbreviations: CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve VEL, velpatasvir

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

Costs for the clinical management of CHC are made up of two main components: 1) Health state costs and 2) treatment-related costs.

Health state costs capture the average medical costs for a representative cohort of patients in a specific health state. Costs include those associated with the management of progressive liver disease (in patients who do not respond to treatment) and with post-treatment surveillance following treatment cessation and achievement of SVR.

Treatment-related costs consist of drug acquisition costs multiplied by the mean treatment duration from trials, and costs associated with on-treatment monitoring for response and adverse events to treatment.

It is expected that the drug costs of the intervention and the comparator regimens will be excluded from the Payment by Results tariff as they will be classified as high cost drugs.

Where costs used are from NHS reference costs or the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care; this is detailed in the later sections.

B.3.5.1 Intervention and comparators' costs and resource use

Costs associated with each treatment regimen, monitoring and treatment-related AEs are summarised in Table 79. Treatment regimen costs were sourced from the British National Formulary (2016; Table 80),[178] and the cost per course of therapy was calculated as the sum product of the daily cost of each component of the regimen and the mean actual duration of treatment (Table 70).

Table 79: Summary of treatment cost inputs

Variable	Base-case value	Source	Comparison to TA430[1]
Regimen costs (per day, 2016 £)			
G/P (list price, indicative)	£464.06	AbbVie	Regimen costs were sourced from the BNF
OBV/PTV/RTV + DSV (list price)	£416.67	BNF (2016)[178]	
OBV/PTV/RTV (list price)	£383.33		
EBR/GZR (list price)	£434.52		

Variable	Base-case value	Source	Comparison to TA430[1]
SOF/LDV (list price)	£464.05		
SOF/VEL (list price)	£464.05		
SOF (list price)	£416.46		
DCV (list price)	£291.88		
RBV (list price)	£13.21		
Peg-IFN (list price)	£17.77		
Monitoring costs (2015/2016 £) – see Table 81			
8 weeks – all-oral therapy	£303	Shepherd et al. (2007)[95] costs inflated to 2015/2016 values[179]	Monitoring costs were also based on Shepherd et al. (2007)[95]
12 weeks – all-oral therapy	£420		
16 weeks – all-oral therapy	£477	Assume equal to 12 weeks monitoring costs + week 8 assessment (£57.52)	
24 weeks – all-oral therapy	£840	Assume proportional to 12 weeks	
Treatment-related AE costs (2015/2016 £)			
Anaemia	£486	Thorlund et al. (2012)[180]	See Table 84
Rash	£160		
Depression	£490	NICE CG90 (2009)[181]	
Grade 3/4 neutropoenia	£1,334	TA430[1]	
Grade 3/4 thrombocytopenia	£1,902		

Abbreviations: AE, adverse event; BNF, British National Formulary; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GZR, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; VEL, velpatasvir

Table 80: Unit costs associated with each treatment in the economic model, from BNF (2016)[178]

Variable	Treatment dosing regimen	Pack size	Pack price	Duration of treatment course (weeks [days])	Course price	Base-case value (cost per day, 2016 £)
G/P	G/P (300 mg/120 mg) OD	28 tablets	£12,993.66	8 (56)	[redacted]	[redacted]
				12 (84)	[redacted]	
				16 (112)	[redacted]	
OBV/PTV/RTV + DSV	OBV 12.5 mg/PTV 75 mg/RTV 50 mg BD	56 tablets	£11,666.66	12 (84)	£34,999.98	£416.67

Variable	Treatment dosing regimen	Pack size	Pack price	Duration of treatment course (weeks [days])	Course price	Base-case value (cost per day, 2016 £)
	DSV 250 mg BD	56 tablets		24 (168)	£69,999.96	
OBV/PTV/RTV	OBV 12.5 mg/PTV 75 mg/RTV 50 mg BD	56 tablets	£10,733.33	12 (84)	£32,199.99	£383.33
EBR/GZR	EBR 50 mg/GZR 100 mg OD	28 tablets	£12,166.67	12 (84)	£36,500.00	£434.52
SOF/LDV	SOF 400 mg/LDV 90 mg OD	28 tablets	£12,993.33	8 (56)	£25,986.66	£464.05
				12 (84)	£38,979.99	
SOF/VEL	SOF 400 mg/VEL 100 mg OD	28 tablets	£12,993.33	12 (84)	£38,980.00	£464.05
SOF	SOF 400 mg OD	28 tablets	£11,660.98	12 (84)	£34,982.94	£416.46
				24 (168)	£69,965.88	
DCV	DCV 60 mg OD	28 tablets	£8,172.61	12 (84)	£24,517.83	£291.88
				24 (168)	£49,035.66	
RBV	1,200 mg per day	56 tablets of 400 mg	£246.65	12 (84)	£1,109.64	£13.21
				24 (168)	£2,219.28	
Peg-IFN	180 µg per week	1 syringe	£124.40	12 (84)	£1,492.80	£17.77
				24 (168)	£2,985.60	

Abbreviations: BD, twice-daily; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GZR, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; OD, once-daily; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; VEL, velpatasvir

Protocols describing the frequency of monitoring of patients whilst being treated with peg-IFN were developed for previous assessment by Shepherd et al. (2007) based on clinical practice at Southampton University Hospital Trust.[95] These protocols were subsequently referenced by Hartwell et al. (2011) and in NICE submissions, including TA430.[1, 17, 100] Consistent with previous assessments in CHC, this economic model also references these assumptions regarding the intensity and quantities of resources associated with patient monitoring when on peg-IFN-based regimens. These assumptions were adapted for DAA regimens to reflect treatment with a peg-IFN-free regimen, and also the shortened treatment duration. Costs were inflated to 2015/2016 values using the PSSRU pay and prices inflation index.[179] Calculations of monitoring costs are described in Table 81. Unlike TA430, monitoring costs are not stratified by cirrhosis status, and there are no monitoring costs for untreated patients.[1] These assumptions are consistent with the economic model submitted previously by AbbVie for OBV/PTV/RTV ± DSV for TA365.[100]

Table 81: Monitoring costs

Resource item form Shepherd et al. (2007)[95]	Unit cost from Shepherd et al. (2007)[95]	Unit cost (2015/16)	Unit cost source
BASELINE			
1st treatment appointment			
Time with nurse - 120 minutes (Grade H assumed)	£33.13	£104.00	PSSRU 2016 Community nurse advanced, band 7 (equivalent to grade H), 2 x cost per hour including qualifications[179, 182]
Time with doctor - 10 minutes (consultant assumed)	£7.72	£22.50	PSSRU 2016 Hospital consultant medical, (1/6) x cost per hour including qualifications[182]
Overheads for clinic administration (pulling notes etc.)	£3.58	£4.26	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179, 182]
Staff costs for outpatient appointment	*£44.43*	*£130.76*	*Sum*
Full blood count	£2.20	£3.10	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179, 182]
Internal normalised ratio	£2.40	£2.85	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS 6inflation indices[179, 182]
Urea & electrolytes	£5.60	£6.66	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices. [179, 182] Note this differs from the NICE HBV Guideline[183] cost (0.80) - used the Shepherd et al (2007)[95] cost as it is closer to that reported by Wright et al. (2006)[94]
Liver function tests	£3.60	£3.10	2013 NICE HBV Guideline (CG165)[183] - based on expert opinion
HCV quantitative viral load	£152.27	£41.35	2013 NICE HBV Guideline (CG165)[183] - based on expert opinion in consultation with UK laboratory managers (assumes PCR)
Pregnancy test (5% of patients)	£0.25	£0.30	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179, 182]
Total for baseline treatment appointment	***£210.75***	***£188.12***	***Sum***
Subsequent appointments			
Basic checks (weeks 1, 2, 6, with pregnancy test at weeks 16 + 20)			

Resource item form Shepherd et al. (2007)[95]	Unit cost from Shepherd et al. (2007)[95]	Unit cost (2015/16)	Unit cost source
Time with nurse - 30 minutes (Grade H assumed)	£8.28	£26.00	PSSRU 2016 Community nurse advanced, band 7 (equivalent to grade H), 0.5 x cost per hour[179]
Time with doctor - 5 minutes (consultant assumed)	£3.86	£11.25	PSSRU 2016 Hospital consultant medical, (5/60) x cost per hour including qualifications[179]
Overheads for clinic administration (pulling notes etc.)	£3.58	£4.26	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Staff costs	*£15.72*	*£41.51*	*Sum*
Full blood count	£2.20	£3.10	NHS reference costs 2015/16 - Directly Accessed Pathology Services (Haematology) - DAPS05[184]
Urea & electrolytes	£5.60	£6.66	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices.[179] Note this differs from the NICE HBV Guideline[183] cost (0.80) - used the Shepherd et al (2007)[95] cost as it is closer to that reported by Wright et al. (2006)[94]
Liver function tests	£3.60	£3.10	NHS reference costs 2015/16 - Directly Accessed Pathology Services (Haematology) - DAPS05[184]
Pregnancy test (weeks 16 + 20)	£0.25	£0.30	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Total for each basic assessment	***£27.37***	***£54.67***	***Sum***
More detailed assessment (at week 4)			
Time with nurse - 30 minutes (Grade H assumed)	£8.28	£26.00	PSSRU 2016 Community nurse advanced, band 7 (equivalent to grade H), 0.5 x cost per hour[179]
Time with doctor - 5 minutes (consultant assumed)	£3.86	£11.25	PSSRU 2016 Hospital consultant medical, (5/60) x cost per hour including qualifications[179]
Overheads for clinic administration (pulling notes etc.)	£3.58	£4.26	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Staff costs	*£15.72*	*£41.51*	*Sum*

Resource item form Shepherd et al. (2007)[95]	Unit cost from Shepherd et al. (2007)[95]	Unit cost (2015/16)	Unit cost source
Full blood count	£2.20	£3.10	NHS reference costs 2015/16 - Directly Accessed Pathology Services (Haematology) - DAPS05[184]
Urea & electrolytes	£5.60	£6.66	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices.[179] Note this differs from the NICE HBV Guideline[183] cost (0.80) - used the Shepherd et al (2007)[95] cost as it is closer to that reported by Wright et al. (2006)[94]
Liver function tests	£3.60	£3.10	NHS reference costs 2015/16 - Directly Accessed Pathology Services (Haematology) - DAPS05[184]
Internal normalised ratio (blood clotting)	£2.40	£2.85	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Pregnancy test (5% of patients)	£0.25	£0.30	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Total for week 4	***£29.77***	***£57.52***	***Sum***
More detailed assessment (at week 8)			
Time with nurse - 30 minutes (Grade H assumed)	£8.28	£26.00	PSSRU 2016 Community nurse advanced, band 7 (equivalent to grade H), 0.5 x cost per hour[179]
Time with doctor - 5 minutes (consultant assumed)	£3.86	£11.25	PSSRU 2016 Hospital consultant medical, (5/60) x cost per hour including qualifications[179]
Overheads for clinic administration (pulling notes etc.)	£3.58	£4.26	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Staff costs	*£15.72*	*£41.51*	*Sum*
Full blood count	£2.20	£3.10	NHS reference costs 2015/16 - Directly Accessed Pathology Services (Haematology) - DAPS05[184]
Urea & electrolytes	£5.60	£6.66	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices.[179] Note this differs from the NICE HBV Guideline[183] cost (0.80) - used the Shepherd et al (2007) [95] cost as it is closer to that reported by Wright et al. (2006)[94]

Resource item form Shepherd et al. (2007)[95]	Unit cost from Shepherd et al. (2007)[95]	Unit cost (2015/16)	Unit cost source
Liver function tests	£3.60	£3.10	NHS reference costs 2015/16 - Directly Accessed Pathology Services (Haematology) - DAPS05[184]
Internal normalised ratio (blood clotting)	£2.40	£2.85	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Pregnancy test (5% of patients)	£0.25	£0.30	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Total for week 8	***£29.77***	***£57.52***	***Sum***
Detailed assessment (week 12)			
Time with nurse - 30 minutes (Grade H assumed)	£8.28	£26.00	PSSRU 2016 Community nurse advanced, band 7 (equivalent to grade H), 0.5 x cost per hour[179]
Time with doctor - 10 minutes (consultant assumed)	£7.72	£22.50	'PSSRU 2015/16 Hospital consultant medical, (1/6) x cost per hour including qualifications[179]
Overheads for clinic administration (pulling notes etc.)	£3.58	£4.26	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Staff costs	*£19.58*	*£52.76*	*Sum*
Full blood count	£2.20	£3.10	NHS reference costs 2015/16 - Directly Accessed Pathology Services (Haematology) - DAPS05[184]
Urea & electrolytes	£5.60	£6.66	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices.[179] Note this differs from the NICE HBV Guideline[183] cost (0.80) - used the Shepherd et al (2007) [95] cost as it is closer to that reported by Wright et al. (2006)[94]
Liver function tests	£3.60	£3.10	NHS reference costs 2015/16 - Directly Accessed Pathology Services (Haematology) - DAPS05[184]
Internal normalised ratio (blood clotting)	£2.40	£2.85	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
TFT (thyroid function tests)	£13.30	£5.08	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices.[179] This cost was chosen as it more closely matched

Resource item form Shepherd et al. (2007)[95]	Unit cost from Shepherd et al. (2007)[95]	Unit cost (2015/16)	Unit cost source
			that reported by Shepherd et al (2007)[95] and Wright et al. (2006),[94] and was recently validated by experts on the Hepatitis B guideline group
Alpha fetoprotein (cirrhotic patients - 15%)	£1.31	£1.56	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
HCV quantitative viral load	£152.27	£41.35	Based on 2013 NICE HBV Guideline (CG165)[183] - based on expert opinion in consultation with UK laboratory managers (assumes PCR) and inflated the cost to 2015/16 using PSSRU 2016 HCHS inflation indices[179]
Pregnancy test (5% of patients)	£0.25	£0.30	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Total for week 12	***£200.51***	***£116.76***	***Sum***
Detailed assessment (week 24)			
Time with nurse - 30 minutes (Grade H assumed)	£8.28	£26.00	PSSRU 2016 Community nurse advanced, band 7 (equivalent to grade H), 0.5 x cost per hour[179]
Time with doctor - 15 minutes (consultant assumed)	£11.59	£33.75	PSSRU 2016 Hospital consultant medical, (15/60) x cost per hour including qualifications[179]
Overheads for clinic administration (pulling notes etc.)	£3.58	£4.26	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
Staff cost	*£23.45*	*£64.01*	*Sum*
Full blood count	£2.20	£3.10	NHS reference costs 2015/16 - Directly Accessed Pathology Services (Haematology) - DAPS05[184]
Urea & electrolytes	£5.60	£6.66	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices.[179] Note this differs from the NICE HBV Guideline[183] cost (0.80) - used the Shepherd et al (2007)[95] cost as it is closer to that reported by Wright et al. (2006)[94]
Liver function tests	£3.60	£3.10	NHS reference costs 2015/16 - Directly Accessed Pathology Services (Haematology) - DAPS05[184]

Resource item form Shepherd et al. (2007)[95]	Unit cost from Shepherd et al. (2007)[95]	Unit cost (2015/16)	Unit cost source
Internal normalised ratio (blood clotting)	£2.40	£2.85	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
TFT (thyroid function tests)	£13.30	£5.08	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices.[179] This cost was chosen as it more closely matched that reported by Shepherd et al (2007)[95] and Wright et al. (2006),[94] and was recently validated by experts on the Hepatitis B guideline group
Alpha fetoprotein (cirrhotic patients - 15%)	£1.31	£1.56	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
HCV qualitative viral load	£11.33	£6.20	Based on 2013 NICE HBV Guideline (CG165)[183] - based on expert opinion in consultation with UK laboratory managers (assumes PCR) and inflated the cost to 2015/16 using PSSRU 2016 HCHS inflation indices[179]
Liver ultrasound	£7.20	£81.67	Based on Backx et al. (2014)[185] and inflated using PSSRU 2016 HCHS indices[179]
Pregnancy test (5% of patients)	£0.25	£0.30	Shepherd et al. (2007)[95] cost inflated using PSSRU 2016 HCHS inflation indices[179]
HCV quantitative viral load	£152.27	£41.35	Based on 2013 NICE HBV Guideline (CG165)[183] - based on expert opinion in consultation with UK laboratory managers (assumes PCR) and inflated the cost to 2015/16 using PSSRU 2016 HCHS inflation indices[179]
Total for week 24	***£222.91***	***£215.88***	***Sum***

Abbreviations: HBV, hepatitis B virus; HCHS, Hospital and Community Health Service; HCV, hepatitis C virus; PCR, polymerase chain reaction; PSSRU, Personal Social Services Research Unit; TFT, thyroid function tests

[

B.3.5.2 Health-state unit costs and resource use

Costs associated with each health state are summarised in Table 82. Health state costs were sourced from Hartwell et al. (2011),[17] and a retrospective analysis of health resource usage and costs by patients in the East Midland region of the UK by Backx et al. (2014).[185] In the study by Backx et al. (2014), data were captured for different disease states (e.g. fibrosis versus cirrhosis) and evaluated according to response to treatment (SVR or non-SVR).[185] Therefore, values from this study were used for SVR health states and F2–F4 health states. It is conservatively assumed that all recovered patients require life-long monitoring post achieving an SVR, irrespective of their initial fibrosis stage. In the absence of more recent or relevant sources, costs for F1 health states and those for more advanced liver disease (DCC, HCC, LT) were sourced from Hartwell et al. (2011).[17] Costs were inflated to 2015/2016 values using the PSSRU pay and prices inflation index.[179] Compared to TA430, this model uses more recent inputs whenever possible from Backx et al. (2014),[185] in line with TA365,[100] whereas the majority of inputs for TA430 are from Wright et al. (2006).[94]

Table 82: Summary of health state costs

Variable	Base-case value	Source	TA430 value and reference[1]
Health state costs (2015/2016 £)			**(2014/2015 £)**
F0	£164	Hartwell et al. (2011)[17]	£327 Calculation: 83%,17% split[a] Wright et al. (2006)[94] Mild: £189 (inflated) Moderate: £1,001 (inflated)
F1	£164		
F2	£609	Backx et al. (2014)[185]	
F3	£609		
CC	£945		£1,561 Wright et al. (2006)[94]
SVR, history of mild fibrosis(F0–F1)	£60	Backx et al. (2014)[185]	£246 Calculation: 83%,17% split[a] Grishchenko et al. (2009)[105] SVR, mild: £237 (inflated) SVR, moderate: £290 (inflated)
SVR, history of moderate fibrosis (F2–F3)	£60		
SVR, history of CC	£606		£513 Grishchenko et al. (2009)[105]
DCC	£12,670	Hartwell et al. (2011)[17]	£12,510 Wright et al. (2006)[94]
HCC	£11,291		£11,147 Wright et al. (2006)[94]
LT (first year)	£51,108		1st year LT: £85,191; 1st year post LT 0-12 months: £28,067; subsequent year £4,194 (12-24 months). From Singh/Longworth et al. (2014);[18] split between post-liver transplant year 1 and year 2 cost based on Wright et al. (2006)[94]
LT (subsequent year)	£1,924		

[a]Based on 83% F0-F2 (mild) and 17% F3 (moderate), derived from HCV TherapyWatch market research data.
Abbreviations: AE, adverse event; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; SVR, sustained virologic response

B.3.5.3 Adverse reaction unit costs and resource use

Frequencies of AEs for each treatment were previously described in Section B.3.3.1. For anaemia and rash, resource use and unit cost were obtained from a UK budget impact analysis by Thorlund et al. (2012) and costs were inflated to 2015/2016 values using the PSSRU pay and prices inflation index.[179, 180] For depression, assumptions used to inform the cost of treatment and monitoring were obtained from NICE GC 90: Depression in adults.[181] These inputs are in line with TA365.[100] Finally, neutropaenia and thrombocytopaenia are based on NICE TA430.[1] The assumptions used to calculate these costs are described in Table 83. There are differences in AE costs in this model compared to TA430, as described in Table 84; because the values for neutropaenia and thrombocytopaenia are based on TA430, these are the same and are therefore not included in Table 84.

Table 83: Treatment-related AE costs

Element	Quantity	% of patients	Cost per unit (2015/2016)[a]	Average cost per item per patient[b]	Source
Anaemia					
Clinic visits	2	100%	£25.84	£51.69	Thorlund et al. (2012)[180]
Erythropoietin treatment	8 weeks	20%	£258.44 per week	£413.51	
Blood transfusion	1	5%	£413	£20.68	
Average per patient treated for anaemia (sum)				*£483.87*	*Calculated*
Rash					
Clinic visits	2	100%	£25.84	£51.69	Thorlund et al. (2012)[180]
Dermatologist visit	1	100%	£77.53	£77.53	
Hydrocortisone 1% cream	2-month supply	100%	£31.01 for 2-month supply	£31.01	
Average per patient treated for rash (sum)				*£160.23*	*Calculated*
Depression					
For moderate depression: Primary care (2 initial visits and every 2 months thereafter for a total of 8 months)	5	50%	£41.60	£104.01	NICE GC 90[181]
For severe depression: specialist setting (2 initial visits and every 2 months thereafter for a total of 8 months)	5	50%	£150.23	£375.58	NICE GC 90[181]
Anti-depression treatment (citalopram)	40 mg/day for 8 months	100%	£1.21 for 28-tab pack of 40 mg tablets	£10.49	BNF (2016)[178]
Average per patient treated for depression (sum)				*£490.08*	*Calculated*
Neutropoenia					
Clinic visits	6	100%	£41.55	£249.27	NICE TA430[1]
Specialist care	1	50%	£223.35	£113.16	

Element	Quantity	% of patients	Cost per unit (2015/2016)[a]	Average cost per item per patient[b]	Source
Neuprogen® (filgratism) Injection (Singleject®)	395 µg/day for 2 weeks	100%	£52.70 for 0.5-mL prefilled syringe 600µg/mL	£971.44	NICE TA430[1] and BNF (2016)[178]
Average per patient treated for neutropaenia (sum)				*£1,333.87*	*Calculated*
Thrombocytopaenia					
Clinic visits	6	100%	£41.55	£249.27	NICE TA430[1]
Specialist care	1	50%	£223.35	£113.16	
Revolade® (eltrombopag)	50 mg/day for 4 weeks	100%	£1,540.00 for 28-tab pack of 50 mg tablets	£1,540.00	NICE TA430[1] and BNF (2016)[178]
Average per patient treated for thrombocytopaenia (sum)				£1,902.43	*Calculated*

[a]The PSSRU pay and prices inflation index was used to adjust prices to the 2015/2016 reference period.[179] Thorlund et al. (2012)[180] prices are assumed to fall in the 2012/2013 reference period, so an inflation correction of 1.03376 was applied. NICE GC90[181] costs are from the 2007/2008 reference period, so an inflation correction of 1.15564 was applied. Prices presented in NICE TA430[1] are assumed to fall in the 2014/2015 reference period, so an inflation correction of 1.10331 is applied to all items except treatments, for which an updated price based on the BNF (2016) was applied;[178] [b]Average cost per item per patient is weighted according to percentage of patients receiving treatment

Abbreviations: AE, adverse event; BNF, British National Formulary; PSSRU, Personal Social Services Research Unit

Table 84: Treatment-related AE costs: comparison to TA430

Assumptions used in this model	Assumptions used in TA430[1]
Anaemia	
Average per patient treated: £483.87	Base-case value: £10.50 (Epo), £8.04 (blood transfusion)
• 2 x clinic visits (£25.84 each) • 20% of patients receiving erythropoietin treatment for 8 weeks (£258.44 per week) • 5% patients receive blood transfusion (£413 per transfusion)	• Erythropoietin – 100% outpatient 6 visits hospital day ward (£41 each) – KOL opinion • Blood transfusion – 50% have consultant-led costs for hepatology (£223.35) – KOL opinion • 0.7% receive blood transfusion (cost £7.26)
Rash	
Average per patient treated: £160.23	Base-case value: £611.95
• 2 x clinic visits (£25.84 each) • 1 x dermatologist visit (£77.53 each) • 100% of patient receive hydrocortisone 1% cream 2-month supply (£31.01 for 2-month supply)	• 100% patients treated as outpatients, 4 hospital, day ward visits (£41 each) – KOL opinion • 100% patients have 2 x specialist visit, consultant led cost for hepatology (£223 each) – KOL opinion

	• 100% patient's hydrocortisone cream 4-week supply (£0.31 per week)
Depression	
Average per patient treated: £490	Base-case value: £110.35
• 50% of patients suffer from moderate depression: treated in primary care, 2 initial visits and every 2 months thereafter for a total of 8 months (£41.60 each) • 50% of patients suffer from moderate severe depression: treated in specialist setting, 2 initial visits and every 2 months thereafter for a total of 8 months (£150.23 each) • All patients receive anti-depression treatment 8 months (citalopram; £10.49 total cost per patient)	• 100% patients have 8 GP visits (£13.67 each) – KOL opinion • Anti-depression treatment 4 weeks citalopram (£0.26 per week)

Note: The values for neutropaenia and thrombocytopaenia in this model are based on TA430; therefore they are the same and are not included in the table above.
Abbreviations: AE, adverse event; GP, general practitioner; KOL, key opinion leader

B.3.5.4 Miscellaneous unit costs and resource use

Not applicable.

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

B.3.6.1 Summary of base-case analysis inputs

The base-case model inputs have been previously described in the following sections:

- Patient characteristics: Table 61 Section B.3.3.1
- Transition probabilities:
  - Treatment phase: SVR rates Table 65 and Table 66 Section B.3.3.2
  - Post-treatment natural disease progression: Table 75 Section B.3.3.3
- AE rates: Table 68 and Table 69 Section B.3.3.2
- Treatment duration: Table 70 Section B.3.3.2
- Health state utilities: Table 77 Section B.3.4.5
- Treatment-related change in health utility: Table 78 Section B.3.4.5

B.3.6.2 Assumptions

Key assumptions informing the model are summarised in Table 85.

Table 85: Assumptions in the economic model analysis

Assumption	Justification
Patients were segmented by fibrosis stage at baseline into mild fibrosis, moderate fibrosis and CC. SVR was conditioned on this segmentation.	Previous models have shown that the cost-effectiveness of treatment strategies is affected by initial fibrosis stage.[98] Previous economic models presented to NICE (TA364 and TA413) have taken this approach.[101, 102]
All treatment effects occur in the first model cycle.	The longest therapy duration for G/P is 16 weeks.
The multiple sequelae related to DCC (i.e., ascites, variceal haemorrhage, hepatic encephalopathy) were combined into a single state.	Sub-manifestations of DCC are not mutually exclusive and an attempt to split out DCC into those sub-health states presents a challenge for the Markov model where a patient can only occupy one health state at a time. Hartwell et al. (2011) and Shepherd et al. (2007) had the same approach.[17, 95]
Patients in DCC and HCC are assumed to be candidates for liver transplantation.	For DCC, Hartwell et al. (2011) and Shepherd et al. (2007) had the same approach.[17, 95] For HCC, Liu et al. (2012) and Johnson et al. (2016) had the same approach.[98, 99]
Background mortality is assumed to be the same as for the general population.	Hartwell et al. (2011) and Shepherd et al. (2007) had the same approach.[17, 95]
Spontaneous remission is not included in the model.	Only patients who develop CHC, and therefore have not successfully cleared the infection, enter the Markov model.
SVR is assumed to be a permanent condition with no spontaneous reactivation of disease.	Hartwell et al. (2011) and Shepherd et al. (2007) had the same approach,[17, 95] and this a widely accepted concept.[111]
Patients with an SVR and a history of CC have an excess risk of HCC. Mild and moderate patients have the same risk of developing HCC as the general population.	Whereas clinical evidence shows that patients who achieve SVR with history of mild or moderate fibrosis have the risk of developing HCC as the general population,[112, 113] patients who achieve SVR with a history of CC still face a risk of developing HCC even after achieving SVR.[112-117] Hartwell et al. (2011) and Shepherd et al. (2007) had the same approach.[17, 95]
Re-infection and onward transmission are not modelled.	Omitting both re-infection and onward transmission represents a conservative approach that likely under-estimates the cost-effectiveness of active treatments including G/P (see Section B.3.2.2.4)
Discontinuation is based on the trials, and trial-based expected treatment duration is assumed, allowing for drop-outs.	There are no real-world data are available for a valid comparison of discontinuation across products. Compared to assuming no drop-outs, allowing trial-based drop-outs is more realistic and conservative. One could argue that it reflects to some extent real-world adherence.
Treatment duration is computed separately for each component of a given therapy.	This is a more realistic and conservative way to measure the length of treatment duration (and eventually therapy cost), as it breaks treatment duration down into its components.
Hazard rates underlying transitional probabilities are constant.	Hartwell et al. (2011) and Shepherd et al. (2007) had the same approach.[17, 95]

Assumption	Justification
Patients on treatment are assumed to experience an effect on HRQoL as a result of treatment AEs. Treatment-related changes in health utility are applied additively to baseline health state health utilities. Treatment-related change in health utility is annualised, and assumed to end at the end of treatment.	Hartwell et al. (2011) and Wright et al. (2006) had the same approach.[17, 94]
Patients who achieve SVR experience an improvement over baseline HRQoL.	Wright et al. (2006) also made this assumption.[94]
No diagnostic or sub-genotyping costs.	Patients entering the model in cycle 1 at the point when a treatment decision is being made, and hence they have already been diagnosed with HCV infection. At the point of diagnosis, patients will have HCV genotype/sub-genotype tested and confirmed. Furthermore, G/P is anticipated to be licensed across genotypes and may therefore provide a treatment option for which patient genotyping is less important and can be excluded from the diagnostics.
On-treatment monitoring costs are dependent on length of treatment duration, at fixed time points (e.g. week 4, 8, 12, etc.).	Based on UK practice patterns.
Assume AEs that are not reported for a given therapy do not occur.	Trials vary in their threshold for AE reporting across publications, our assumption of zero AE for those not reported is conservative.
Assume that AEs are regimen and genotype specific, but independent of fibrosis severity for F0–F3.	This is the level of detail available from the trials.

Abbreviations: AE, adverse event; CC, compensated cirrhosis; CHC, chronic hepatitis C; DCC, decompensated cirrhosis; G/P, glecaprevir/pibrentasvir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HRQoL, health-related quality of life; SVR, sustained virologic response

B.3.7 *Base-case results*

Base-case incremental cost-effectiveness analysis results are presented with patients stratified by genotype, treatment history and cirrhosis status. Patients are also stratified by IFN-eligibility for GT2 TN patients, in line with NICE TA treatment recommendations and clinical practice. Therefore in total there are therefore 26 separate subgroups for which base-case results are presented (TN NC, TN CC, TE NC and TE CC for each of the six genotypes, with GT2 TN NC and GT2 TN CC divided into IFN-eligible and IFN-ineligible). List price was used for G/P and all comparators. Results are presented in Sections B.1.1.1.1 through B.3.7.1.6, and are summarised in Table 86.

The base-case cost-effectiveness analysis applied list prices for G/P and all comparators. At a cost-effectiveness threshold of £20,000 per QALY gained, G/P was cost-effective in 13 of 26 subgroups. In 12 of these subgroups G/P was associated with the lowest total costs, being dominant in 4 of these.

In considering these results it should be noted that several comparators have PAS price agreements, and a confidential pricing agreement with CMU for G/P is currently under

negotiation. Therefore the prices used in the base-case, and the resulting ICERs, are not a realistic representation of the cost-effectiveness of G/P.

A pricing scenario analysis exploring the base-case incremental cost-effectiveness analysis results using a price for G/P in line with the proposed confidential pricing agreement with CMU (see Section B.3.8.3).

In the sections that follow, 'dominated' refers to the case where a treatment is associated with a higher cost and a lower or identical QALY gain compared to G/P.

Table 86: Summary of base-case incremental cost-effectiveness analysis results (list price)

GT	Treatment history	Cirrhosis status	Result
GT1	TN	NC	In the two GT1 NC populations, G/P is cost-effective versus no treatment with ICERs <£3,200. All other regimens are dominated. In the GT1 TN CC population, G/P has an ICER of £12,927 per QALY gained versus EBR/GZR, which has an ICER of £4,778 versus no treatment. All other regimens are dominated. In the GT1 TE CC population, G/P is dominated by SOF/VEL. SOF/VEL has an ICER of £7,928 versus EBR/GZR, which has an ICER of £5,423 versus no treatment. All other regimens are dominated
		CC	
	TE	NC	
		CC	
GT2	TN	NC	In the IFN-eligible population, G/P has an ICER of £36,936 versus peg-IFN + RBV In the IFN-ineligible population, G/P is cost-effective treatment versus no treatment (ICER of £5,620), with all other regimens either dominated or with an ICER far above the conventional cost-effectiveness threshold in the incremental analysis
		CC	In both the IFN-eligible and IFN-ineligible populations, G/P is dominated by SOF/VEL, which has an ICER of £5,243 versus no treatment in both populations. The other treatment option in the IFN-ineligible population (SOF + RBV) is extendedly dominated
	TE	NC	G/P is cost-effective versus no treatment (ICER of £5,813) with all other regimens either dominated or with an ICER far above the conventional cost-effectiveness threshold in the incremental analysis
		CC	G/P is dominated by SOF/VEL, which has an ICER of £5,561 versus no treatment. The other treatment option (SOF + RBV) is also dominated.
GT3	TN	NC	In all GT3 TN populations, G/P is cost-effective versus no treatment (ICERs <£5,200), with all other regimens either dominated or with an ICER far above the conventional cost-effectiveness threshold in the incremental analysis
		CC	
	TE	NC	G/P has an ICER of £167,731 versus SOF + peg-IFN + RBV, which has an ICER of £5,396 versus no treatment. All other treatments are dominated
		CC	G/P has an ICER of £92,584 versus SOF/VEL, which has an ICER of £6,537 versus no treatment. All other regimens are either dominated or have an ICER far above the conventional cost-effectiveness threshold in the incremental analysis

GT4	**TN**	**NC**	G/P is cost-effective versus no treatment (ICER of £4,039), with all other regimens either dominated or with an ICER >£20,000
		CC	G/P is dominated by SOF/VEL. OBV/PTV/RTV is cost-effective versus no treatment (ICER of £3,451). EBR/GZR has an ICER of £29,607 versus OBV/PTV/RTV, and SOF/VEL has an ICER of £373,179 versus EBR/GZR. SOF/LDV is also dominated by SOF/VEL
	TE	**NC**	G/P is cost-effective versus no treatment (ICER of £2,938), with all other regimens either dominated or with an ICER far above the conventional cost-effectiveness threshold in the incremental analysis
		CC	G/P is dominated by SOF/VEL. OBV/PTV/RTV is cost-effective versus no treatment (ICER of £3,465). SOF/VEL has an ICER of £113,791 versus OBV/PTV/RTV
GT5	**TN**	**NC**	G/P is cost-effective versus no treatment (ICER of £3,347), with SOF/VEL dominated by G/P
		CC	G/P is dominated by SOF/VEL. SOF/VEL has an ICER of £5,121 versus no treatment; SOF + peg-IFN + RBV is also dominated by SOF/VEL
	TE	**NC**	G/P is cost-effective versus no treatment (ICER of £2,938); the ICER of SOF/VEL versus G/P is far above the conventional cost-effectiveness threshold
		CC	G/P is dominated by SOF/VEL. The ICER of SOF/VEL versus no treatment is £5,398; SOF + peg-IFN + RBV is also dominated by SOF/VEL
GT6	**TN**	**NC**	G/P is cost-effective versus no treatment (ICER of £4,534) at a cost-effectiveness threshold of £20,000; the ICER of SOF/VEL versus G/P is £28,640
		CC	G/P is dominated by SOF/VEL. SOF/VEL has an ICER of £5,121 versus no treatment; SOF + peg-IFN + RBV is also dominated by SOF/VEL
	TE	**NC**	G/P is cost-effective versus no treatment (ICER of £2,938); the ICER of SOF/VEL versus G/P is far above the conventional cost-effectiveness threshold
		CC	G/P is dominated by SOF/VEL. The ICER of SOF/VEL is £5,398; SOF + peg-IFN + RBV is also dominated by SOF/VEL

Abbreviations: CC, compensated cirrhosis; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; GZR, grazoprevir; ICER, incremental cost-effectiveness ratio; IFN, interferon; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; peg-IFN, pegylated IFN; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

B.3.7.1.1 GT1 patients

TN patients

Table 87: Base-case incremental cost-effectiveness analysis results for GT1 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	19,514	18.77	12.66	N/A	N/A	N/A	N/A	N/A	54,584
G/P	29,708	20.27	15.90	10,194	1.501	3.239	3,147	3,147	N/A
SOF/LDV	**30,404**	**20.21**	**15.77**	**10,890**	**1.438**	**3.105**	**3,507**	**Dominated**	**3,367**
OBV/PTV/RTV + DSV	39,733	20.25	15.84	20,218	1.474	3.176	6,367	Dominated	11,291
EBR/GZR	41,156	20.19	15.71	21,641	1.413	3.046	7,105	Dominated	15,303
SOF/VEL	42,899	20.26	15.88	23,385	1.491	3.222	7,257	Dominated	13,522

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 88: Base-case incremental cost-effectiveness analysis results for GT1 TN CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	43,322	13.35	7.13	N/A	N/A	N/A	N/A	N/A	44,602
EBR/GZR	**57,032**	**17.00**	**10.00**	**13,711**	**3.659**	**2.870**	**4,778**	**4,778**	**916**
G/P	58,706	17.16	10.13	15,384	3.815	2.999	5,129	12,927	N/A
SOF/VEL	58,962	17.11	10.09	15,640	3.763	2.958	5,287	Dominated	1,076
SOF/LDV	59,801	16.94	9.95	16,479	3.591	2.816	5,851	Dominated	4,754
OBV/PTV/RTV + DSV	80,032	17.02	10.01	36,711	3.676	2.880	12,749	Dominated	23,722

Abbreviations: CC, compensated cirrhosis; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

TE patients

Table 89: Base-case incremental cost-effectiveness analysis results for GT1 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	20,977	17.99	11.92	N/A	N/A	N/A	N/A	N/A	55,036
G/P	29,819	19.67	15.11	8,842	1.684	3.194	2,768	2,768	N/A
OBV/PTV/RTV + DSV	**39,870**	**19.64**	**15.04**	**18,893**	**1.653**	**3.125**	**6,045**	**Dominated**	**11,424**
EBR/GZR	41,332	19.57	14.92	20,355	1.584	3.003	6,779	Dominated	15,338
SOF/VEL	43,047	19.66	15.09	22,070	1.670	3.172	6,957	Dominated	13,657
SOF/LDV	43,650	19.61	14.99	22,673	1.619	3.068	7,390	Dominated	16,347

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

Table 90: Base-case incremental cost-effectiveness analysis results for GT1 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	42,629	13.18	7.04	N/A	N/A	N/A	N/A	N/A	38,459
EBR/GZR	57,130	16.55	9.72	14,501	3.372	2.674	5,423	5,423	-517
SOF/VEL	**58,428**	**16.75**	**9.88**	**15,799**	**3.570**	**2.838**	**5,568**	**7,928**	**-2,493**
G/P	59,212	16.64	9.79	16,583	3.462	2.752	6,026	Dominated	N/A
SOF/LDV	61,428	16.30	9.52	18,799	3.126	2.479	7,585	Dominated	7,686

OBV/PTV/RTV + DSV	78,973	16.74	9.87	36,343	3.567	2.824	12,868	Dominated	18,315

Abbreviations: CC, compensated cirrhosis; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

B.3.7.1.2 GT2 patients

TN patients

Table 91: Base-case incremental cost-effectiveness analysis results for GT2 TN NC patients (IFN-eligible)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
peg-IFN + RBV	**11,126**	**20.19**	**15.50**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**-8,245**
No treatment	15,238	19.49	13.52	4,113	-0.701	-1.981	-2,076	Dominated	35,493
G/P	29,108	20.34	15.99	17,983	0.149	0.487	36,936	36,936	N/A

Abbreviations: G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; peg-IFN, pegylated IFN; QALY, quality-adjusted life year; RBV, ribavirin; TN, treatment-naïve

Table 92: Base-case incremental cost-effectiveness analysis results for GT2 TN NC patients (IFN-ineligible)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	15,238	19.49	13.52	N/A	N/A	N/A	N/A	N/A	35,493
G/P	29,108	20.34	15.99	13,870	0.850	2.468	5,620	5,620	N/A
SOF + RBV	**39,349**	**20.32**	**15.92**	**24,111**	**0.828**	**2.399**	**10,049**	**Dominated**	**11,618**
SOF/VEL	42,172	20.34	16.00	26,934	0.851	2.475	10,881	1,823,564	12,921

Abbreviations: G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 93: Base-case incremental cost-effectiveness analysis results for GT2 TN CC patients (IFN-eligible)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	44,514	13.98	7.48	N/A	N/A	N/A	N/A	N/A	39,568
SOF/VEL	**58,632**	**17.23**	**10.17**	**14,119**	**3.252**	**2.693**	**5,243**	**5,243**	**-168**
G/P	58,800	17.23	10.17	14,286	3.252	2.693	5,305	Dominated	N/A

Abbreviations: CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; QALY, quality-adjusted life year; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 94: Base-case incremental cost-effectiveness analysis results for GT2 TN CC patients (IFN-ineligible)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	44,514	13.98	7.48	N/A	N/A	N/A	N/A	N/A	39,568
SOF + RBV	58,068	16.89	9.88	13,554	2.916	2.407	5,631	Extended dominance	4,977
SOF/VEL	**58,632**	**17.23**	**10.17**	**14,119**	**3.252**	**2.693**	**5,243**	**5,243**	**-168**
G/P	58,800	17.23	10.17	14,286	3.252	2.693	5,305	Dominated	N/A

Abbreviations: CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

TE patients

Table 95: Base-case incremental cost-effectiveness analysis results for GT2 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)

No treatment	17,098	18.69	12.72	N/A	N/A	N/A	N/A	N/A	32,393
G/P	30,369	19.65	15.00	13,271	0.960	2.283	5,813	5,813	N/A
SOF + RBV	41,046	19.62	14.92	23,948	0.930	2.203	10,870	Dominated	12,280
SOF/VEL	**42,223**	**19.74**	**15.22**	**25,125**	**1.051**	**2.504**	**10,035**	**53,745**	**7,443**

Abbreviations: G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

Table 96: Base-case incremental cost-effectiveness analysis results for GT2 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	43,738	13.78	7.37	N/A	N/A	N/A	N/A	N/A	37,087
SOF/VEL	**58,088**	**16.86**	**9.95**	**14,350**	**3.075**	**2.580**	**5,561**	**5,561**	**-168**
G/P	58,255	16.86	9.95	14,517	3.075	2.580	5,626	Dominated	N/A
SOF + RBV	60,940	16.16	9.36	17,202	2.376	1.983	8,676	Dominated	14,634

Abbreviations: CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

B.3.7.1.3 GT3 patients

TN patients

Table 97: Base-case incremental cost-effectiveness analysis results for GT3 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	22,440	18.03	11.92	N/A	N/A	N/A	N/A	N/A	66,164
G/P	30,956	20.11	15.65	8,516	2.075	3.734	2,281	2,281	N/A

SOF/VEL	**43,243**	**20.18**	**15.78**	**20,804**	**2.146**	**3.865**	**5,382**	**93,521**	**9,660**
SOF + DCV	63,992	20.15	15.72	41,553	2.117	3.805	10,921	Dominated	31,618

Abbreviations: DCV, daclatasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; QALY, quality-adjusted life year; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 98: Base-case incremental cost-effectiveness analysis results for GT3 TN CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	42,077	12.69	6.78	N/A	N/A	N/A	N/A	N/A	48,468
G/P	58,948	17.02	10.04	16,871	4.333	3.267	5,164	5,164	N/A
SOF + peg-IFN + RBV	59,129	16.71	9.77	17,053	4.019	2.990	5,704	Dominated	5,728
SOF/VEL	**59,158**	**16.94**	**9.98**	**17,081**	**4.255**	**3.208**	**5,324**	**Dominated**	**1,383**
SOF + RBV	95,637	16.10	9.32	53,561	3.415	2.545	21,045	Dominated	51,128
SOF + DCV	132,691	17.09	10.06	90,614	4.402	3.285	27,588	4,192,135	73,391

Abbreviations: CC, compensated cirrhosis; DCV, daclatasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; peg-IFN, pegylated IFN; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

TE patients

Table 99: Base-case incremental cost-effectiveness analysis results for GT3 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	23,577	17.28	11.23	N/A	N/A	N/A	N/A	N/A	39,633
SOF + peg-IFN + RBV	**42,864**	**19.49**	**14.81**	**19,286**	**2.207**	**3.574**	**5,396**	**5,396**	**-12,569**
SOF/VEL	44,725	19.42	14.73	21,148	2.135	3.499	6,045	Dominated	-9,190
G/P	57,135	19.52	14.89	33,557	2.235	3.659	9,170	167,731	N/A

SOF + DCV	64,681	19.48	14.83	41,104	2.204	3.596	11,430	Dominated	8,813

Abbreviations: DCV, daclatasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; peg-IFN, pegylated IFN; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

Table 100: Base-case incremental cost-effectiveness analysis results for GT3 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	41,467	12.54	6.70	N/A	N/A	N/A	N/A	N/A	28,930
SOF + peg-IFN + RBV	59,878	16.13	9.39	18,411	3.590	2.691	6,841	Extended dominance	-6,488
SOF/VEL	**60,190**	**16.30**	**9.56**	**18,724**	**3.764**	**2.864**	**6,537**	**6,537**	**-9,631**
G/P	72,475	16.48	9.69	31,008	3.942	2.997	10,347	92,584	N/A
SOF + RBV	99,328	15.01	8.55	57,862	2.473	1.853	31,229	Dominated	49,735
SOF + DCV	132,173	16.73	9.85	90,706	4.188	3.153	28,772	383,284	56,583

Abbreviations: CC, compensated cirrhosis; DCV, daclatasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; peg-IFN, pegylated IFN; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

B.3.7.1.4 GT4 patients

TN patients

Table 101: Base-case incremental cost-effectiveness analysis results for GT4 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	18,786	18.90	12.81	N/A	N/A	N/A	N/A	N/A	46,237
G/P	30,487	20.19	15.71	11,701	1.293	2.897	4,039	4,039	N/A
OBV/PTV/RTV	**37,000**	**20.30**	**15.95**	**18,214**	**1.401**	**3.137**	**5,806**	**27,142**	**1,714**
EBR/GZR	39,972	20.30	15.94	21,186	1.401	3.135	6,759	Dominated	4,732

SOF/VEL	42,556	20.30	15.95	23,770	1.401	3.141	7,567	1,203,376	7,178

Abbreviations: EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 102: Base-case incremental cost-effectiveness analysis results for GT4 TN CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	43,442	13.41	7.17	N/A	N/A	N/A	N/A	N/A	44,096
OBV/PTV/RTV	**53,347**	**17.04**	**10.04**	**9,905**	**3.633**	**2.870**	**3,451**	**3,451**	**-3,398**
EBR/GZR	56,058	17.17	10.13	12,616	3.759	2.962	4,260	29,607	-2,519
SOF/VEL	58,642	17.17	10.14	15,200	3.759	2.968	5,121	373,179	-73
G/P	58,715	17.17	10.14	15,273	3.759	2.968	5,145	Dominated	N/A
SOF/LDV	58,780	17.17	10.13	15,338	3.759	2.962	5,179	Dominated	203

Abbreviations: CC, compensated cirrhosis; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LDV, ledipasvir; LYG, life years gained; N/A, not applicable; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

TE patients

Table 103: Base-case incremental cost-effectiveness analysis results for GT4 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	20,320	18.11	12.05	N/A	N/A	N/A	N/A	N/A	52,870
G/P	29,425	19.70	15.15	9,105	1.588	3.099	2,938	2,938	N/A
OBV/PTV/RTV	**37,133**	**19.70**	**15.14**	**16,814**	**1.588**	**3.091**	**5,440**	**Dominated**	**7,871**
EBR/GZR	40,089	19.70	15.15	19,770	1.588	3.095	6,387	Dominated	10,734

SOF/VEL	42,692	19.70	15.16	22,373	1.588	3.102	7,212	3,858,701	13,199
SOF/LDV	45,441	19.45	14.67	25,122	1.344	2.619	9,592	Dominated	25,610

Abbreviations: EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LDV, ledipasvir; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir TE, treatment-experienced; VEL, velpatasvir

Table 104: Base-case incremental cost-effectiveness analysis results for GT4 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	42,741	13.24	7.08	N/A	N/A	N/A	N/A	N/A	41,498
OBV/PTV/RTV	**52,432**	**16.74**	**9.87**	**9,691**	**3.502**	**2.797**	**3,465**	**3,465**	**-4,752**
SOF/VEL	58,109	16.80	9.92	15,368	3.565	2.847	5,398	113,791	-73
G/P	58,182	16.80	9.92	15,441	3.565	2.847	5,424	Dominated	N/A
SOF/LDV	58,247	16.80	9.92	15,506	3.565	2.840	5,460	Dominated	203
EBR/GZR	63,500	15.61	8.97	20,759	2.377	1.893	10,964	Dominated	24,390

Abbreviations: CC, compensated cirrhosis; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LDV, ledipasvir; LYG, life years gained; N/A, not applicable; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

B.3.7.1.5 GT5 patients

TN patients

Table 105: Base-case incremental cost-effectiveness analysis results for GT5 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	18,786	18.90	12.81	N/A	N/A	N/A	N/A	N/A	52,258
G/P	29,289	20.30	15.95	10,503	1.401	3.138	3,347	3,347	N/A
SOF/VEL	**43,093**	**20.25**	**15.84**	**24,307**	**1.352**	**3.033**	**8,013**	**Dominated**	**15,898**

Abbreviations: G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; QALY, quality-adjusted life year; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 106: Base-case incremental cost-effectiveness analysis results for GT5 TN CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	43,442	13.41	7.17	N/A	N/A	N/A	N/A	N/A	44,096
SOF/VEL	**58,642**	**17.17**	**10.14**	**15,200**	**3.759**	**2.968**	**5,121**	**5,121**	**-73**
G/P	58,715	17.17	10.14	15,273	3.759	2.968	5,145	Dominated	N/A
SOF + peg-IFN + RBV	69,422	15.29	8.62	25,980	1.879	1.447	17,960	Dominated	41,144

Abbreviations: CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; peg-IFN, pegylated IFN; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

TE patients

Table 107: Base-case incremental cost-effectiveness analysis results for GT5 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	20,320	18.11	12.05	N/A	N/A	N/A	N/A	N/A	52,870
G/P	29,425	19.70	15.15	9,105	1.588	3.099	2,938	2,938	N/A
SOF/VEL	**42,692**	**19.70**	**15.16**	**22,373**	**1.588**	**3.102**	**7,212**	**3,858,701**	**13,199**

Abbreviations: G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; QALY, quality-adjusted life year; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

Table 108: Base-case incremental cost-effectiveness analysis results for GT5 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	42,741	13.24	7.08	N/A	N/A	N/A	N/A	N/A	41,498
SOF/VEL	**58,109**	**16.80**	**9.92**	**15,368**	**3.565**	**2.847**	**5,398**	**5,398**	**-73**
G/P	58,182	16.80	9.92	15,441	3.565	2.847	5,424	Dominated	N/A
SOF + peg-IFN + RBV	68,805	15.02	8.46	26,064	1.782	1.386	18,807	Dominated	39,845

Abbreviations: CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; peg-IFN, pegylated IFN; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

B.3.7.1.6 GT6 patients

TN patients

Table 109: Base-case incremental cost-effectiveness analysis results for GT6 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	18,786	18.90	12.81	N/A	N/A	N/A	N/A	N/A	42,474
G/P	31,236	20.12	15.55	12,450	1.225	2.746	4,534	4,534	N/A
SOF/VEL	**42,556**	**20.30**	**15.95**	**23,770**	**1.401**	**3.141**	**7,567**	**28,640**	**3,415**

Abbreviations: G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; QALY, quality-adjusted life year; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 110: Base-case incremental cost-effectiveness analysis results for GT6 TN CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	43,442	13.41	7.17	N/A	N/A	N/A	N/A	N/A	44,096

SOF/VEL	**58,642**	**17.17**	**10.14**	**15,200**	**3.759**	**2.968**	**5,121**	**5,121**	**-73**
G/P	58,715	17.17	10.14	15,273	3.759	2.968	5,145	Dominated	N/A
SOF + peg-IFN + RBV	69,422	15.29	8.62	25,980	1.879	1.447	17,960	Dominated	41,144

Abbreviations: CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; peg-IFN, pegylated IFN; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

TE patients

Table 111: Base-case incremental cost-effectiveness analysis results for GT6 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	20,320	18.11	12.05	N/A	N/A	N/A	N/A	N/A	52,870
G/P	29,425	19.70	15.15	9,105	1.588	3.099	2,938	2,938	N/A
SOF/VEL	**42,692**	**19.70**	**15.16**	**22,373**	**1.588**	**3.102**	**7,212**	**3,858,701**	**13,199**

Abbreviations: G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; NC, non-cirrhotic; QALY, quality-adjusted life year; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

Table 112: Base-case incremental cost-effectiveness analysis results for GT6 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	INMB of G/P versus comparator (£)
No treatment	42,741	13.24	7.08	N/A	N/A	N/A	N/A	N/A	41,498
SOF/VEL	**58,109**	**16.80**	**9.92**	**15,368**	**3.565**	**2.847**	**5,398**	**5,398**	**-73**
G/P	58,182	16.80	9.92	15,441	3.565	2.847	5,424	Dominated	N/A
SOF + peg-IFN + RBV	68,805	15.02	8.46	26,064	1.782	1.386	18,807	Dominated	39,845

Abbreviations: CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; INMB, incremental net monetary benefit; LYG, life years gained; N/A, not applicable; peg-IFN, pegylated IFN; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; VEL, velpatasvir

B.3.8 *Sensitivity analyses*

Baseline demographics (e.g. genotype distribution, fibrosis distribution, age, percentage male, treatment history [treatment-naïve vs -experienced]), background death rate, discount rates, regimen duration and costs, and treatment monitoring costs) were not varied in the deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). Background death rate is based on large national samples with little measurement error. Drug costs are endogenous, and no data were identified for varying regimen duration, which came from trials.

The variables tested in the DSA and PSA are described in Appendix Section L.1.2. All PSA and DSA analyses were performed using the list price for each comparator, including G/P.

B.3.8.1 Probabilistic sensitivity analysis

B.3.8.1.1 Methods

PSA was undertaken in the analysis in all 26 patient subgroups for which base-case incremental cost-effectiveness analysis results were presented. Given the number of subgroups and the number of comparators within each subgroup, it was not feasible to run a PSA for all comparisons in all patient subgroups. Therefore, for each of the 26 subgroups PSA was run for the comparison of G/P to a single comparator treatment. The comparator selected in each subgroup was the comparator against which the case for cost-effectiveness of G/P was least demonstrated. This was judged as the comparator against which G/P had the lowest incremental net monetary benefit (INMB; issues of dominance rendered the use of ICERs inappropriate to make this judgement; hence the use of INMB) when valuing a QALY at £20,000 per QALY gained (Table 113).

Table 113: Comparators for PSA/DSA analysis

Genotype	Treatment history	Cirrhosis status	Comparator for PSA/DSA analysis
GT1	**TN**	**NC**	SOF/LDV
		CC	EBR/GZR
	TE	**NC**	OBV/PTV/RTV + DSV
		CC	SOF/VEL
GT2	**TN**	**NC**	IFN-eligible: peg-IFN + RBV IFN-ineligible: SOF + RBV
		CC	IFN-eligible: SOF/VEL IFN-ineligible: SOF/VEL
	TE	**NC**	SOF/VEL
		CC	SOF/VEL
GT3	**TN**	**NC**	SOF/VEL
		CC	SOF/VEL
	TE	**NC**	SOF + peg-IFN + RBV
		CC	SOF/VEL
GT4	**TN**	**NC**	OBV/PTV/RTV
		CC	OBV/PTV/RTV
	TE	**NC**	OBV/PTV/RTV

		CC	OBV/PTV/RTV
GT5	**TN**	**NC**	SOF/VEL
		CC	SOF/VEL
	TE	**NC**	SOF/VEL
		CC	SOF/VEL
GT6	**TN**	**NC**	SOF/VEL
		CC	SOF/VEL
	TE	**NC**	SOF/VEL
		CC	SOF/VEL

Abbreviations: CC, compensated cirrhosis; DSA, deterministic sensitivity analysis; DSV, dasabuvir; EBR, elbasvir; GT, genotype; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; PSA, probabilistic sensitivity analysis; PTV, paritaprevir; peg-IFN, pegylated IFN; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

For each PSA, 500 simulations were drawn from the variables' distributions. Results of the PSA were reported as the probability of cost-effectiveness of G/P versus the comparator treatment.

SVR rates were assumed to have a beta distribution, characterised by the trial subgroup sample size and percentage with SVR. Due to the lack of data, PSA variation on treatment-related utility change is only possible for AbbVie G/P; a normal distribution was assumed.

B.3.8.1.2 Results

PSA results are presented in Table 114.

Table 114: PSA results

Genotype	Treatment history	Cirrhosis status	Comparator	Probability of cost-effectiveness of G/P at £20,000 threshold	Probability of cost-effectiveness of G/P at £30,000 threshold
GT1	**TN**	**NC**	SOF/LDV	99.4%	99.2%
		CC	EBR/GZR	57.0%	67.4%
	TE	**NC**	OBV/PTV/RTV + DSV	100.0%	100.0%
		CC	SOF/VEL	12.0%	12.4%
GT2	**TN**	**NC**	IFN-eligible: peg-IFN + RBV	0.4%	18.4%
			IFN-ineligible: SOF + RBV	100.0%	100.0%
		CC	IFN-eligible:* SOF/VEL	41.0%	42.4%
			IFN-ineligible:* SOF/VEL	41.0%	42.4%
	TE	**NC**	SOF/VEL	100.0%	96.8%
		CC	SOF/VEL	38.8%	43.0%
GT3	**TN**	**NC**	SOF/VEL	100.0%	99.6%
		CC	SOF/VEL	73.8%	73.2%

	TE	**NC**	SOF + peg-IFN + RBV	0.0%	0.0%
		CC	SOF/VEL	0.2%	3.4%
GT4	**TN**	**NC**	OBV/PTV/RTV	78.6%	52.8%
		CC	OBV/PTV/RTV	12.6%	22.4%
	TE	**NC**	OBV/PTV/RTV	100.0%	100.0%
		CC	OBV/PTV/RTV	2.4%	6.0%
GT5	**TN**	**NC**	SOF/VEL	100.0%	100.0%
		CC	SOF/VEL	47.4%	48.0%
	TE	**NC**	SOF/VEL	100.0%	100.0%
		CC	SOF/VEL	46.4%	48.6%
GT6	**TN**	**NC**	SOF/VEL	74.4%	57.8%
		CC	SOF/VEL	48.6%	49.4%
	TE	**NC**	SOF/VEL	100.0%	100.0%
		CC	SOF/VEL	46.6%	46.8%

*Note: In GT2 TN CC, the comparator for PSA in the IFN-eligible and IFN-ineligible populations is the same (SOF/VEL). There were no differences in modelling of the IFN-eligible vs IFN-ineligible subgroups (i.e. no differences in model inputs), with the only difference between these subgroups being the comparator list for the incremental analysis. Therefore, when performing analysis in the IFN-eligible vs IFN-ineligible subgroups using the same comparator, the results are identical.
Abbreviations: CC, compensated cirrhosis; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; PSA, probabilistic sensitivity analysis; PTV, paritaprevir; peg-IFN, pegylated IFN; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

B.3.8.2 Deterministic sensitivity analysis

B.3.8.2.1 Methods

The non-treatment-specific variables tested in DSA included transitional probabilities related to disease progression, health state and AE costs, and health utilities (a full list of the parameters varied can be found in described in Appendix Section L.1.2).

Regimen attributes, including SVR and AE rates were also tested in DSA. SVR and AE rates were assumed to vary based on ± 1.96 times their standard deviations.

DSA was undertaken in the analysis in all patient subgroups for which base-case incremental cost-effectiveness analysis results were presented. As for the PSA analysis, given the number of subgroups and the number of comparators within each subgroup, it was not feasible to run a DSA for all comparisons in all patient subgroups. Therefore, for each of subgroups DSA was run for the same comparator as for the PSA.

B.3.8.2.2 Results

Across the vast majority of patient subgroups, INMB was most sensitive to SVR rate for G/P and/or SVR rate for the comparator. Tornado diagrams for the DSA analyses in each subgroup are presented in Appendix Section L.1.3.

B.3.8.3 Scenario analysis

B.3.8.3.1 Methods

Price scenario analysis

A pricing scenario analysis was performed in line with the proposed confidential pricing agreement with CMU for G/P which is under negotiation, which is more representative of the true price of G/P if it were used in clinical practice than the base-case list price. This scenario also applied the CMU price for OBV/PTV/RTV ± DSV. The following changes were applied to the base-case for this scenario:

- [redacted] (Table 115). All other prices were the same as for the base-case.

Table 115: Cost per day for G/P per treatment duration based on discount price for G/P

Treatment duration	Cost per day	Total regimen cost	Patient populations according to anticipated licence (not yet confirmed)
8 weeks	[redacted]	[redacted]	• TN NC patient populations for GT1–6 • TE NC patient populations for GT1, GT2, GT4–6
12 weeks	[redacted]	[redacted]	• TN CC patient populations for GT1–6 • TE CC patient populations for GT1, GT2, GT4–6
16 weeks	[redacted]	[redacted]	• TE NC/CC GT3 patient populations

Abbreviations: CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; NC, non-cirrhotic; TE, treatment-experienced; TN, treatment-naïve

- [redacted].
- The CMU price for OBV/PTV/RTV ± DSV was applied as described in Table 116.

Table 116: Cost per day for OBV/PTV/RTV ± DSV with CMU price

Treatment	Pack price	Course price	Base-case value (cost per day, 2016 £)
OBV/PTV/RTV + DSV	[redacted]	[redacted]	[redacted]
OBV/PTV/RTV	[redacted]	[redacted]	[redacted]

[a]The course price is independent of treatment duration. Therefore the base-case cost per day value for OBV/PTV/RTV + DSV for GT1 CC patients was calculated by taking the weighted average of the daily price for a 12-week treatment duration (GT1b patients) and the daily price for a 24-week duration (GT1a patients), using the GT1a/GT1b distribution described by Harris et al. (1999) in Section B.3.3.1.[121]
Abbreviations: CC, compensated cirrhosis; CMU, Commercial Medicines Unit; DSV, dasabuvir; GT, genotype; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; RTV, ritonavir

An incremental analysis using these assumptions was performed in all 26 patient subgroups for which base-case incremental cost-effectiveness analysis results were presented.

Trial-based health utilities

A scenario analysis was performed in which health state utility values for CHC mild (F0–F1) and moderate (F2–F3) fibrosis and CC states are based on the baseline EQ-5D observations from all Phase III G/P clinical trials, with UK crosswalk applied to all data. This scenario analysis was conducted to to explore the impact of this altenative source of utility values on model results. Data were consolidated for all enrolled HCV-mono-infected patients, regardless of genotype, treatment history, and treatment duration. The difference in health utility between the baseline and post-treatment Week 12 values from the G/P trials is assumed to represent the increment/decrement associated with the recovered states. Health state utilities are described in Table 117.

Table 117: Summary of trial-based health state utilities

Health state	Health state utility value
F0	[redacted]
F1	[redacted]
F2	[redacted]
F3	[redacted]
CC	[redacted]
SVR, history of mild fibrosis (F0, F1)	[redacted]
SVR, history of moderate fibrosis (F2, F3)	[redacted]
SVR, history of CC (F4)	[redacted]
DCC	[redacted]
HCC	[redacted]
LT (first year)	[redacted]
LT (subsequent)	[redacted]

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; SVR, sustained virologic response

An incremental analysis using these assumptions was performed in all 26 patient subgroups for which base-case incremental cost-effectiveness analysis results were presented. List prices were used for all comparators, including G/P.

B.3.8.3.2 Results

Price scenario analysis

Incremental cost-effectiveness analysis results, stratified by genotype, treatment history and cirrhosis status, are presented in Appendix L.1.4.

[redacted]

[redacted]

Trial-based health utilities

Incremental cost-effectiveness analysis results, stratified by genotype, treatment history and cirrhosis status, are presented in Appendix L.1.5.
[redacted]

B.3.8.4 Summary of sensitivity analyses results

When DSA analysis was performed comparing G/P to the comparator against which G/P had the lowest INMB in the base-case in each of the 26 patient subgroups, in the vast majority of subgroups INMB was most sensitive to SVR rate for G/P and/or SVR rate for the comparator (Section B.3.8.2).

In a scenario analysis exploring the base-case incremental cost-effectiveness analysis results using a price for G/P in line with the proposed confidential pricing agreement with CMU (Section B.3.8.3.2),
[redacted].

In the second scenario analysis, using health state utility values for CHC mild (F0–F1) and moderate (F2–F3) fibrosis and CC states based on the baseline EQ-5D observations from all Phase III G/P clinical trials in place of health state utility values from the literature
[redacted]

B.3.9 *Subgroup analysis*

No subgroup analyses were performed as no other subgroups except for those presented in the base-case analysis were deemed relevant to this submission.

B.3.10 *Validation*

B.3.10.1 Technical and internal validation

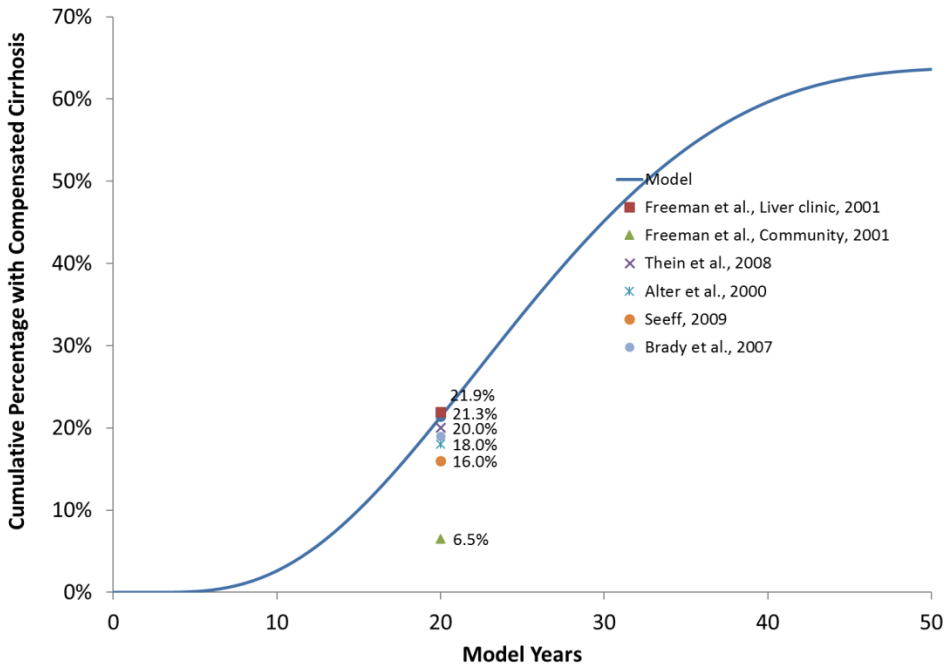
Technical validation involved checking the software programme and cleaning it for potential programming errors. Validation using different routine tests yielded the expected results. Two experienced, independent modelers also reviewed the model structure and parameters. Internal validation involved comparing the model's predictions with the data that was used.

B.3.10.2 External validation: model estimates of CC in untreated patients

To assess external validity of the model, the model's estimates of CC in untreated GT1 patients (i.e. setting treatment to "No Treatment") with F0 (i.e. setting the "initial fibrosis distribution" to 100% F0) were generated. Fibrosis progression rates in the model are derived from Thein et al. (2008).[159] When Thein et al. (2008)'s baseline patient characteristics (age 43, 62% male) are applied, our model predicts 21.3% of patients would have a history of CC 20 years post-infection.

CC rate estimates over 50 years appear in Figure 16, which also includes cirrhosis estimates from other sources.

Figure 16: Model and published estimates of cumulative CC rates



Abbreviation: CC, compensated cirrhosis

Freeman et al. (2001) reported a systematic review of 57 epidemiological studies.[186] Each of the 57 studies had a different mean duration of infection for the study patients, ranging from 3 to 26 years. The authors divided the published studies into four categories per population: liver clinic series, post-transfusion studies, blood donor studies, and community-based studies. The authors estimated the prevalence of cirrhosis at 20 years for each study and then estimated the mean prevalence of cirrhosis for each group of studies. After 20 years of infection with HCV, the mean proportion of cases with cirrhosis was 21.9% in the liver clinic series (N=482), 23.8% in the post-transfusion cohorts (N=72), 3.7% for the blood donor series (N=65), and 6.5% for the community-based cohorts (N=231). The liver clinic series and community-based cohorts are included in Figure 16, given their larger sample sizes.

In addition to Freeman et al. (2001), two clinical literature review articles, Alter and Seeff (2000),[187] Seeff (2009),[188] one systematic meta-analysis, Thein et al. (2008),[159] and one model, Brady et al. (2007),[189] were selected for comparison.

Alter and Seeff (2000) summarised the existing literature on the natural progression of HCV. They found thirteen analyses with varying study designs (i.e. retrospective, prospective, and cohort) which examined the presence of cirrhosis in patients with interval exposure ranging from 7 to 50 years.[187] Of the twelve studies that examined adult patients, rates of cirrhosis varied from 2% to 55% at the end of follow-up. The authors then synthesised the data to provide point estimates for the long-term natural progression of HCV. The progression to a severe clinical outcome, defined as cirrhosis and/or HCC, was approximated at about 20% at 20 years.

A follow-up study by Seeff (2009) estimated cirrhosis in their mild patient cohort 20 years after infection was "16% overall, 18% for cross-sectional/retrospective and 7% for retrospective-prospective studies, 18% for studies in clinical studies and 7% for studies conducted in non-clinical settings."[188]

Other articles indicate a similar progression rate. The progression of untreated HCV infection to cirrhosis is oft-cited to be approximately 20% within 20 years of disease, which is primarily based on figures taken from prospective studies published in the early to mid-1990s.[190-192] In the literature reviews and meta-analyses summarising data from multiple trials, the overall range of progression to cirrhosis varied from 15% to 25% at 20 years follow-up.

Brady et al. (2007) developed a model to project natural progression to cirrhosis for HCV patients for an economic evaluation of peg-IFN plus RBV for CHC treatment.[189] Brady et al. (2007) conducted formal validation analyses. Their model projected a progression to cirrhosis in 19% of HCV patients at 20 years. They also performed a review of published prospective studies to assess external validity, and determined progression to cirrhosis to be about 20% at 20 years among HCV patients.

B.3.11 *Interpretation and conclusions of economic evidence*

There are no prior economic evaluations investigating the cost-effectiveness of G/P in treatment of CHC. This economic evaluation provides the first such analysis, and provides evidence across all six major HCV genotypes in patients with varying degrees of liver damage and with or without a prior history of HCV treatment.

The base-case economic analysis applied list prices for all comparators and G/P. Of 26 subgroups (TN NC, TN CC, TE NC and TE CC for each of 6 genotypes, with GT2 TN NC and CC divided into IFN-eligible and IFN-ineligible), at a cost-effectiveness threshold of £20,000 per QALY gained, G/P was the cost-effective treatment in 13 of the 26 subgroups. In 12 of these subgroups G/P was associated with the lowest total costs, with G/P being dominant in 4 of these. In a pricing scenario analysis in which the price of G/P was aligned with the proposed confidential pricing agreement with the CMU and the CMU price for OBV/PTV/RTV ± DSV was applied,

[redacted].

Important strengths of the evaluation are as follows:

- The model approach, structure and inputs are in line with previous cost-effectiveness analyses in CHC used for NICE appraisals. Therefore, the model uses a well-established approach to describe the natural disease progression of CHC, includes all important health effects of treatment, and whenever possible applies inputs from studies performed in the UK.

- The model comparators were chosen to represent as accurately as possible the current treatment landscape in CHC for each subgroup of patients, in line with NICE guidance, expert clinical advice and the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1).[2]
- The model was validated by two experienced health economists

Weaknesses of the model include:

- It is not feasible to form any network between G/P and any relevant comparator therapies to develop a NMA. Therefore, the economic model relies on SVR rates as reported by individual trials for G/P and comparator therapies for each subgroup. Lack of control arms is a very common feature of clinical trials in hepatitis C across DAAs, so this weakness is shared with the models submitted to NICE for other DAAs, including that of SOF/VEL (TA430).
- Neither re-infection nor onward transmission is included in the model. However, this is in line with previous conclusions by NICE that without a model that incorporates both re-infection and transmission, cost-effectiveness results excluding re-infection and transmission are acceptable for decision making.[97] There is evidence to suggest that incorporating both re-infection and onward transmission has a net positive impact on cost-effectiveness in dynamic transmission models for treatment of HCV infection,[119] the Markov model presented here may represent a conservative approach that under-estimates the cost-effectiveness of active treatments including G/P and the wider societal benefits associated with treatment.

References

1. NICE. Sofosbuvir–velpatasvir for treating chronic hepatitis C: Technology appraisal guidance [TA430], 2017.
2. Eastern Liver Network. Management of Hepatitis C: Hepatitis C Guidelines v 8.1 09 June 2017.
3. Ahmed A, Felmlee DJ. Mechanisms of Hepatitis C Viral Resistance to Direct Acting Antivirals. Viruses 2015;7:6716-29.
4. Chevaliez S, Pawlotsky JM. HCV Genome and Life Cycle. In: Tan SL, ed. Hepatitis C Viruses: Genomes and Molecular Biology. Norfolk (UK): Horizon Bioscience, 2006.
5. Poordad F, Felizarta F, Asatryan A, et al. Glecaprevir and Pibrentasvir for 12 Weeks for HCV Genotype 1 Infection and Prior Direct-acting Antiviral Treatment. Hepatology 2017;Epub ahead of print.
6. Ng TI, Krishnan P, Pilot-Matias T, et al. In Vitro Antiviral Activity and Resistance Profile of the Next Generation Hepatitis C Virus NS5A Inhibitor Pibrentasvir. Antimicrob Agents Chemother 2017.
7. MHRA. Early Access to Medicines Scientific Opinion - Public Assessment Report: Glecaprevir/Pibrentasvir 100mg/40mg film-coated tablets, 2016.
8. Ansaldi F, Orsi A, Sticchi L, et al. Hepatitis C virus in the new era: perspectives in epidemiology, prevention, diagnostics and predictors of response to therapy. World J Gastroenterol 2014;20:9633-52.
9. Public Health England. Hepatitis C in the UK. 2015 Report.
10. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3:47-52.
11. Patruni B, Nolte E. Hepatitis C: A Projection of the Healthcare and Economic Burden in the UK. Rand Health Q 2013;3:6.
12. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014;61:S58-68.
13. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2017;66:153-194.
14. Negro F, Forton D, Craxi A, et al. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology 2015;149:1345-60.
15. Younossi ZM, Kanwal F, Saab S, et al. The impact of hepatitis C burden: an evidence-based approach. Aliment Pharmacol Ther 2014;39:518-31.
16. National Institute for Health and Care Excellence. Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID 921]. 2016.
17. Hartwell D, Jones J, Baxter L, et al. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. Health Technol Assess 2011;15:i-xii, 1-210.
18. Singh J, Longworth L. Estimating The Cost Of Liver Transplantation In Patients Diagnosed With Chronic Hepatitis C And B In the UK. Value Health 2014;17:A368.
19. Vietri J, Prajapati G, El Khoury AC. The burden of hepatitis C in Europe from the patients' perspective: a survey in 5 countries. BMC Gastroenterol 2013;13:16.
20. British Society of Gastroenterology: Clinical Services. Chronic Management: Management of Patients with Chronic Liver Diseases.
21. The Hepatitis C Trust. The uncomfortable truth. Hepatitis C in England: the state of the nation. Available at: http://www.hcvaction.org.uk/sites/default/files/resources/The%20Uncomfortable%20Truth.pdf [Last accessed February 2017]. 2013.
22. Neal KR, Ramsay S, Thomson BJ, et al. Excess mortality rates in a cohort of patients infected with the hepatitis C virus: a prospective study. Gut 2007;56:1098-104.
23. Public Health England. Hepatitis C in the UK. 2017 Report.
24. Venkatesh PG, Parasa S, Njei B, et al. Increased mortality with peptic ulcer bleeding in patients with both compensated and decompensated cirrhosis. Gastrointestinal Endoscopy 2014;79:605-614. e3.
25. Younossi Z, Stepanova M, Saab S, et al. The impact of viral hepatitis-related hepatocellular carcinoma to post-transplant outcomes. Journal of Viral Hepatitis 2016;23:53-61.
26. NICE. NICE Guideline: Hepatitis C In development [GID-CGWAVE0666]. Volume 2017, 2016.

27. Feld JJ, Moreno C, Trinh R, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks. J Hepatol 2016;64:301-7.
28. Asselah T, Hezode C, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin in adults with hepatitis C virus genotype 4 infection and cirrhosis (AGATE-I): a multicentre, phase 3, randomised open-label trial. Lancet Gastroenterol Hepatol 2016;1:25-35.
29. Manos MM, Ho CK, Murphy RC, et al. Physical, social, and psychological consequences of treatment for hepatitis C : a community-based evaluation of patient-reported outcomes. Patient 2013;6:23-34.
30. NICE. Sofosbuvir–velpatasvir for treating chronic hepatitis C: Technology appraisal guidance [TA430]. Resource Impact Template. Available at https://www.nice.org.uk/guidance/ta430/resources. Last accessed 22 March 2017.
31. Adelphi Research UK. Patient tracker, Project reference 22968, 2017.
32. Public Health England. Improving access to, and completion of, hepatitis C treatment, 2015.
33. National Public Health Service for Wales. Chronic hepatitis C - the patients' perspective, 2006.
34. Welsh Assembly Government. Blood Borne Viral Hepatitis Action Plan for Wales 2010-2015, 2010.
35. Welsh Government. Together for Health – Liver Disease Delivery Plan, 2015.
36. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015;61:77-87.
37. Greyson O. Hepatitis C awareness among South Asians. Nurs Times 2012;108:21-3.
38. Gane D, Lawitz E, Pugatch D, et al. EXPEDITION-4: Efficacy and safety of glecaprevir/pibrentasvir (ABT-493/ABT-530) in patients with renal impairment and chronic hepatitis C virus genotype 1-6 infection. AASLD. Boston, MA, 2016.
39. Poordad F, Gordon S, Asatryan A, et al. High efficacy of ABT-493 and ABT-530 in HCV genotype-1 infected patients who have failed direct-acting antiviral-containing regimens: the MAGELLAN-I study. EASL. Barcelona, Spain, 2016.
40. Pilot-Matias T, Krisnan P, Schnell G, et al. Resistance analysis in the MAGELLAN-I study (Part 2): Glecaprevir/pibrentasvir therapy in HCV-infected patients who had failed prior DAA regimens containing NS3/4A protease and/or NS5A inhibitors. EASL. Amsterdam, the Netherlands, 2017.
41. Poordad F, Pol S, Asatryan A, et al. MAGELLAN-1, Part 2: Glecaprevir and pibrentasvir for 12 or 16 weeks in patients with chronic hepatitis C virus genotype 1 or 4 and prior direct-acting antiviral treatment failure. EASL. Amsterdam, the Netherlands, 2017.
42. Rockstroh J, Lacombe K, Viani R, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients co-infected with hepatitis C virus and human immunodeficiency virus-1: the EXPEDITION-2 study. EASL. Amsteram, the Netherlands, 2017.
43. Reau N, Kwo P, Rhee S, et al. MAGELLAN-2: safety and efficacy of glecaprevir/pibrentasvir in liver or renal transplant adults with chronic hepatitis C genotype 1-6 infection. EASL. Amsterdam, the Netherlands, 2017.
44. Zeuzem S, Feld J, Wang S, et al. ENDURANCE-1: A phase 3 evaluation of the efficacy and safety of 8- vs 12-week treatment with glecaprevir/pibrentasvir (formerly ABT-493/ABT-530) in HCV genotype 1-infected patients with or without HIV-1 co-infecition and without cirrhosis. AASLD. Boston, MA, 2016.
45. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Subjects With Genotype 1 Infection Study Record Detail. Available at: https://clinicaltrials.gov/ct2/show/record/NCT02604017?term=endurance-1&rank=2. Last accessed 9 May 2017.
46. AbbVie. Data on File: A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1 Infection (ENDURANCE-1): Clinical Study Report R&D/16/0144 ABT-493/ABT-530 Protocol M13-590 (Primary Analysis), 2016.
47. Kowdley K, Colombi M, Zadeikis N, et al. ENDURANCE-2: Safety and efficacy of glecaprevir/pibrentasvir in hepatitis C virus genotype 2-infected patients without cirrhosis: a randomized, double-blind, placebo-controlled study. AASLD. Boston, MA, 2016.
48. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Subjects With Chronic Hepatitis C Virus (HCV) Genotype 2 Infection Study Record Detail.

Available at: https://clinicaltrials.gov/ct2/show/NCT02640482?term=ENDURANCE-2&rank=1. Last accessed 9 May 2017.
49. AbbVie. Data on File: A Randomized, Double-Blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 2 Infection (ENDURANCE-2): Clinical Study Report R&D/16/0145 ABT-493/ABT-530 Protocol M15-464, 2016.
50. Foster G, Gane E, Asatryan A, et al. ENDURANCE-3: A phase 3, randomized, open-label, active-controlled study to compare efficacy and safety of ABT-493/ABT-530 to sofosbuvir co-administered with daclatasvir in adults with HCV genotype 3 infection. EASL. Barcelona, Spain, 2016.
51. ClinicalTrials.gov. A Study Comparing Efficacy and Safety of ABT-493/ABT-530 to Sofosbuvir Dosed With Daclatasvir in Adults With HCV Genotype 3 Infection (ENDURANCE-3). Available at: https://clinicaltrials.gov/ct2/show/NCT02640157?term=ENDURANCE-3&rank=1. Last accessed 9 May 2017.
52. AbbVie. Data on File: A Randomized, Open-Label, Active-Controlled, Multicenter Study to Compare Efficacy and Safety of ABT-493/ABT-530 to Sofosbuvir Co-Administered with Daclatasvir in Adults with Chronic Hepatitis C Virus Genotype 3 Infection (ENDURANCE-3): Clinical Study Report R&D/16/0162 ABT-493/ABT-530 Protocol M13-594 (Primary Analysis), 2016.
53. Asselah T, Hezode C, Zadeikis N, et al. ENDURANCE-4: Efficacy and safety of glecaprevir/pibrentasvir (formerly ABT-493/ABT-530) treatment in patients with chronic HCV genotype 4, 5 or 6 infection. AASLD. Boston, MA, 2016.
54. ClinicalTrials.gov. The Efficacy and Safety of ABT-493/ABT-530 in Adults With Chronic Hepatitis C Virus Genotype 4, 5, or 6 Infection (ENDURANCE-4). Available at: https://clinicaltrials.gov/ct2/show/NCT02636595?term=ENDURANCE-4&rank=1. Last accessed 9 May 2017.
55. AbbVie. Data on File: A Single-Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 4, 5, or 6 Infection (ENDURANCE-4): Clinical Study Report R&D/16/0157 ABT-493/ABT-530 Protocol M13-583 (Primary Analysis), 2016.
56. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults With Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis (EXPEDITION-1). Available at: https://clinicaltrials.gov/ct2/show/NCT02642432?term=EXPEDITION-1&rank=1. Last accessed 9 May 2017.
57. AbbVie. Data on File: A Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis (EXPEDITION-1): Clinical Study Report R&D/16/0158 ABT-493/ABT-530 Protocol M14-172 (Primary Analysis), 2016.
58. Muir A, Strasser S, Wang S, et al. High SVR rates with ABT-493 + ABT-530 co-administered for 8 weeks in non-cirrhotic patients with HCV genotype 3 infection. EASL. Barcelona, Spain, 2016.
59. Kwo P, Poordad F, Porcalla A, et al. Safety of ABT-493 + ABT-530 co-administered in patients with HCV genotype 1-6 infection: results from SURVEYOR-I and SURVEYOR-II studies. EASL. Barcelona, Spain, 2016.
60. Poordad F, Kwo P, Hassanein T, et al. High SVR rates with ABT-493 + ABT-530 in non-cirrhotic patients with HCV genotypes 1, 2, 3 infection. APASL. Tokyo, Japan, 2016.
61. Kwo P, Bennet M, Wang S, et al. SURVEYOR-II: High SVR4 rates achieved with the next generation NS3/4A protease inhibitor ABT-493 and NS5A inhibitor ABT-530 in non-cirrhotic treatment-naive and treatment-experienced patients with HCV genotype 3 infection. AASLD. San Francisco, CA, 2015.
62. Poordad F, Felizarta F, Wang S, et al. High SVR rates with a combination of ABT-493 + ABT-530 for 8 weeks in non-cirrhotic patients with HCV genotype 1 or 2 infection. EASL. Barcelona, Spain, 2016.
63. ClinicalTrials.gov. A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without RBV in Subjects With Chronic Hepatitis C Virus (HCV) Genotypes 2, 3, 4, 5 or 6 Infection. Available at: https://clinicaltrials.gov/ct2/show/NCT02243293?term=surveyor-ii&rank=1. Last accessed 9 May 2017.

64. AbbVie. Data on File: A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without RBV in Subjects With Chronic Hepatitis C Virus (HCV) Genotypes 2, 3, 4, 5 or 6 Infection (SURVEYOR-II): Clinical Study Report R&D/15/1230 ABT-493, ABT-530, ABT-493/ABT-530 Protocol M14-868 (Primary Analysis), 2016.
65. Wyles D, Poordad F, Wang S, et al. SURVEYOR-II, Part 3: Efficacy and Safety of glecaprevir/pibrentasvir (ABT-493/ABT-530) in patients with hepatitis C virus genotype 3 infection with prior treatment experience and/or cirrhosis. AASLD. Boston, MA, 2016.
66. AbbVie. Data on File: An Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without Ribavirin in Subjects with Chronic Hepatitis C Virus (HCV) Genotype 1, 4, 5, and 6 Infection (SURVEYOR-I): Clinical Study Report R&D/15/1229 ABT-493, ABT-530 Protocol M14-867, 2016.
67. ClinicalTrials.gov. A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-administration of ABT-493 and ABT-530 With and Without Ribavirin in Subjects With HCV Genotype 1, 4, 5, and 6 Infection. Available at: https://clinicaltrials.gov/ct2/show/NCT02243280?term=surveyor-i&rank=1. Last accessed 9 May 2017.
68. Gane E, Lalezari J, Asatryan A, et al. 100% SVR4 and favorable safety of ABT-493 + ABT-530 administered for 12 weeks in non-cirrhotic patients with genotypes 4, 5, or 6 infection (SURVEYOR-I). EASL. Barcelona, Spain, 2016.
69. Wyles D, Sulkowski M, Wang S, et al. SURVEYOR-II: High SVR4 rates achieved with next generation NS3/4A protease inhibitor ABT-493 and NS5A inhibitor ABT-530 in non-cirrhotic treatment-naive and treatment-experienced patients with HCV genotype 2 infection. AASLD. San Francisco, CA, 2015.
70. Hassanein T, Wyles D, Wang S, et al. SURVEYOR-II, Part 4: Glecaprevir/pibrentasvir demonstrates high SVR rates in patients with HCV genotype 2, 4, 5, or 6 infection without cirrhosis following an 8-week treatment duration. AASLD. Bostom, MA, 2016.
71. AbbVie. Data on File: A Single-Arm, Open-Label, Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Renally-Impaired Adults with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (EXPEDITION-4): Clinical Study Report R&D/16/0159 ABT-493/ABT-530 Protocol M15-462 (Primary Analysis), 2016.
72. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Renally Impaired Adults With Chronic Hepatitis C Virus Genotype 1 - 6 Infection (EXPEDITION-4). Available at: https://clinicaltrials.gov/ct2/show/NCT02651194?term=expedition-4&rank=1. Last accessed 9 May 2017.
73. AbbVie. Data on File: A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 (or ABT-493/ABT-530) With and Without Ribavirin in Adults With Chronic Hepatitis C Virus (HCV) Infection Who Failed a Prior Direct-Acting Antiviral Agent (DAA)-Containing Therapy: Clinical Study Report R&D/16/0160 ABT-493, ABT-530, ABT-493/ABT-530 Protocol M15-410 (Primary Analysis), 2016.
74. ClinicalTrials.gov. A Study to Evaluate the Safety and Efficacy of ABT-493/ABT-530 in Adult Post-Liver or Post-Renal Transplant Recipients With Chronic Hepatitis C Virus (MAGELLAN-2). Available at: https://clinicaltrials.gov/ct2/show/NCT02692703?term=magellan-2&rank=1. Last accessed 9 May 2017.
75. AbbVie. Data on File: A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Japanese Adults with Chronic Hepatitis C Virus Infection (CERTAIN-1) Interim Clinical Study Report R&D/16/0779 ABT-493/ABT-530/Protocol M15-594, 2017.
76. Chayama K, Suzuki F, Karino Y, et al. CERTAIN-1: Efficacy and Safety of Glecaprevir/Pibrentasvir in Japanese Patients with Chronic Genotype 1 Hepatitis C Virus Infection with and without Cirrhosis. EASL. Amsterdam, the Netherlands, 2017.
77. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Japanese Adults With Chronic Hepatitis C Virus Infection (CERTAIN-1). Available at: https://clinicaltrials.gov/ct2/show/NCT02707952?term=certain-1&rank=1. Last accessed 9 May 2017.

78. Chayama K, Suzuki F, Sato K, et al. Efficacy and Safety of Glecaprevir/Pibrentasvir in Japanese Patients with Chronic Genotype 2 Hepatitis C Virus Infection with and without Cirrhosis. EASL. Amsterdam, the Netherlands, 2017.
79. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Japanese Adults With Genotype 2 Chronic Hepatitis C Virus Infection (CERTAIN-2). Available at: https://clinicaltrials.gov/ct2/show/NCT02723084?term=certain+2&rank=1. Last accessed 9 May 2017.
80. AbbVie. Data on File: A Randomized, Open-Label, Active Comparator, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Japanese Adults with Genotype 2 Chronic Hepatitis C Virus Infection (CERTAIN-2) Interim Clinical Study Report R&D/16/1258 ABT-493/ABT-530/Protocol M15-828, 2017.
81. Bristol-Myers Squibb Company. Daklinza® (daclatasvir) Tablets [package insert], 2015.
82. Gilead Sciences Inc. Harvoni® (ledipasvir and sofosbuvir tablet) [package insert], 2015.
83. Gilead Sciences Inc. Sovaldi® (sofosbuvir tablet) [package insert], 2015.
84. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial. Ann Intern Med 2015;163:1-13.
85. Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. Lancet HIV 2015;2:e319-27.
86. AbbVie. Data on File: Clinical Study Protocol M14-730 A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection and Human Immunodeficiency Virus-1 (HIV-1) Co-Infection (EXPEDITION-2), 2016.
87. AbbVie. Data on File: Clinical Study Protocol M13-596 A Single-Arm, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of ABT-493/ABT-530 in Adult Post-Liver or Post-Renal Transplant Recipients with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (MAGELLAN-2), 2016.
88. Foster G, Gane E, Asatryan A, et al. ENDURANCE-3: safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naïve HCV genotype 3-infected patients without cirrhosis. EASL. Amsterdam, the Netherlands, 2017.
89. Forns X, Lee S, Valdes J, et al. EXPEDITION-I: Efficacy and safety of glecaprevir/pibrentasvir in adults with chronic hepatitis C virus genotype 1, 2, 4, 5 or 6 infection and compensated cirrhosis. EASL. Amsterdam, the Netherlands, 2017.
90. AbbVie. Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir) tablets [package insert]. 2015.
91. Puoti M, Foster GR, Wang S, et al. High SVR rates with eight and twelve weeks of pangenotypic glecaprevir/pibrentasvir: integrated efficacy analysis of genotypes 1-6 patients without cirrhosis. EASL. Amsterdam, the Netherlands, 2017.
92. Gilead Sciences Ltd. Epclusa 400 mg/100 mg film coated tablets summary of product characteristics. Available at: https://www.medicines.org.uk/emc/medicine/32177. Last accessed 12 May 2017.
93. AbbVie. Data on File: Glecaprevir/Pibrentasvir Summary of Clinical Efficacy, 2016.
94. Wright M, Grieve R, Roberts J, et al. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess 2006;10:1-113, iii.
95. Shepherd J, Jones J, Hartwell D, et al. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess 2007;11:1-205, iii.
96. NICE. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C [TA200], 2010.
97. NICE. Final appraisal determination: Sofosbuvir–velpatasvir for treating chronic hepatitis C, 2016.
98. Liu S, Cipriano LE, Holodniy M, et al. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Ann Intern Med 2012;156:279-90.
99. Johnson SJ, Parise H, Virabhak S, et al. Economic evaluation of ombitasvir/paritaprevir/ritonavir and dasabuvir for the treatment of chronic genotype 1 hepatitis c virus infection. J Med Econ 2016;19:983-94.
100. NICE. Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C: Technology appraisal guidance [TA365], 2015.

101. NICE. Elbasvir–grazoprevir for treating chronic hepatitis C: Technology appraisal guidance [TA413], 2016.
102. NICE. Daclatasvir for treating chronic hepatitis C: Technology appraisal guidance [TA364], 2015.
103. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463-72.
104. Sangiovanni A, Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. Hepatology 2006;43:1303-10.
105. Grishchenko M, Grieve RD, Sweeting MJ, et al. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. Int J Technol Assess Health Care 2009;25:171-80.
106. Salomon JA, Weinstein MC, Hammitt JK, et al. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. JAMA 2003;290:228-37.
107. Grieve R, Roberts J, Wright M, et al. Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. Gut 2006;55:1332-8.
108. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. Clin Infect Dis 2011;52:889-900.
109. Morisco F, Granata R, Stroffolini T, et al. Sustained virological response: a milestone in the treatment of chronic hepatitis C. World J Gastroenterol 2013;19:2793-8.
110. Papastergiou V, Stampori M, Lisgos P, et al. Durability of a sustained virological response, late clinical sequelae, and long-term changes in aspartate aminotransferase to the platelet ratio index after successful treatment with peginterferon/ribavirin for chronic hepatitis C: a prospective study. Eur J Gastroenterol Hepatol 2013;25:798-805.
111. Koh C, Heller T, Haynes-Williams V, et al. Long-term outcome of chronic hepatitis C after sustained virological response to interferon-based therapy. Aliment Pharmacol Ther 2013;37:887-94.
112. Veldt BJ, Saracco G, Boyer N, et al. Long term clinical outcome of chronic hepatitis C patients with sustained virological response to interferon monotherapy. Gut 2004;53:1504-8.
113. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303-13.
114. Lee SH, Jin YJ, Shin JY, et al. Assessment of hepatocellular carcinoma risk based on peg-interferon plus ribavirin treatment experience in this new era of highly effective oral antiviral drugs. Medicine (Baltimore) 2017;96:e5321.
115. Janjua NZ, Chong M, Kuo M, et al. Long-term effect of sustained virological response on hepatocellular carcinoma in patients with hepatitis C in Canada. J Hepatol 2017;66:504-513.
116. Aleman S, Rahbin N, Weiland O, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infect Dis 2013;57:230-6.
117. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010;52:833-44.
118. Pitman R, Fisman D, Zaric GS, et al. Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-5. Med Decis Making 2012;32:712-21.
119. Madin-Warburton. M, Pitcher A, Martin N. The impact of dynamic transmission modelling on the estimated cost-effectiveness of treatment for chronic hepatitis C in the UK. Presentation MO3. ISPOR. Vienna, Austria, 2016.
120. NICE. Guide to the methods of technology appraisal 2013. Volume Vol PMG9, 2013.
121. Harris KA, Gilham C, Mortimer PP, et al. The most prevalent hepatitis C virus genotypes in England and Wales are 3a and 1a. J Med Virol 1999;58:127-31.
122. (ONS) OfNS. National life tables for the UK, based on data for the years 2013-2015. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/20132015. Last accessed 9 May 2017.
123. AbbVie. Data on File: AGATE-I CSR.
124. Hezode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet 2015;385:2502-9.

125. AbbVie. Data on File: PEARL-I CSR.
126. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014;147:359-365 e1.
127. AbbVie. Data on File: PEARL-II CSR.
128. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983-92.
129. AbbVie. Data on File: PEARL-III CSR.
130. AbbVie. Data on File: PEARL-IV CSR.
131. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973-82.
132. AbbVie. Data on File: TURQUOISE-II CSR.
133. AbbVie. Data on File: TURQUOISE-III CSR.
134. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594-603.
135. AbbVie. Data on File: SAPPHIRE-I CSR.
136. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1604-14.
137. AbbVie. Data on File: SAPPHIRE-II CSR.
138. Kwo P, Gane EJ, Peng CY, et al. Effectiveness of Elbasvir and Grazoprevir Combination, With or Without Ribavirin, for Treatment-Experienced Patients With Chronic Hepatitis C Infection. Gastroenterology 2017;152:164-175 e4.
139. FDA. ZEPATIER™ Full Prescribing Information, 2016.
140. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889-98.
141. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483-93.
142. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014;370:1879-88.
143. Abergel A, Asselah T, Metivier S, et al. Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. Lancet Infect Dis 2016;16:459-64.
144. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med 2015;373:2599-607.
145. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med 2015;373:2608-17.
146. Jacobson IM, Lawitz E, Gane EJ, et al. Efficacy of 8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir in Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. Gastroenterology 2017;153:113-122.
147. Foster GR, Zeuzem S, Gane E, et al. Sofosbuvir-Based Regimens for Patients with Chronic Hepatitis C Genotype 3 Infection: Integrated Analysis of Five Clinical Studies AASLD. Boston, MA, 2016.
148. Foster GR, Pianko S, Brown A, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. Gastroenterology 2015;149:1462-70.
149. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014;370:1993-2001.
150. EMC. Sovaldi 400 mg film coated tablets Summary of Produce Charactieristics. Available at: https://www.medicines.org.uk/emc/medicine/28539. Last accessed 14 June 2016.
151. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;368:1867-77.
152. Stepanova M, Nader F, Cure S, et al. Patients' preferences and health utility assessment with SF-6D and EQ-5D in patients with chronic hepatitis C treated with sofosbuvir regimens. Alimentary Pharmacology and Therapeutics 2014;40:676-685.
153. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. Lancet Infect Dis 2013;13:401-8.

154. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878-87.
155. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology 2015;61:1127-35.
156. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370:211-21.
157. NICE. Telaprevir for the treatment of genotype 1 chronic hepatitis C: Technology appraisal guidance [TA252], 2011.
158. Abergel A, Metivier S, Samuel D, et al. Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. Hepatology 2016;64:1049-56.
159. Thein HH, Yi Q, Dore GJ, et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48:418-31.
160. NICE. Boceprevir for the treatment of genotype 1 chronic hepatitis C [TA253], 2012.
161. Public Health England. Hepatitis C in the UK. 2014 Report.
162. Westin J, Nordlinder H, Lagging M, et al. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. J Hepatol 2002;37:837-42.
163. Kanwal F, Kramer JR, Ilyas J, et al. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. Hepatology 2014;60:98-105.
164. Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol 2010;52:652-7.
165. Siebert U, Sroczynski G, Rossol S, et al. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. Gut 2003;52:425-32.
166. Siebert U, Sroczynski G, Wasem J, et al. Using competence network collaboration and decision-analytic modeling to assess the cost-effectiveness of interferon alpha-2b plus ribavirin as initial treatment of chronic hepatitis C in Germany. Eur J Health Econ 2005;6:112-23.
167. NHS Organ Donation and Transplantation. Policy POL195/4: Liver Transplantation: Selection Criteria and Recipient Registration 2015.
168. Cheung M, Foster G, Irving W, et al. Antiviral treatment in patients with advanced HCV cirrhosis using sofosbuvir and ledipasvir/ daclatasvir, with or without ribavirin – outcomes compared to untreated patients and long term outcomes. Presented at EASL. Barcelona., 2016.
169. Bennett WG, Inoue Y, Beck JR, et al. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. Ann Intern Med 1997;127:855-65.
170. The EuroQol Group. EQ-5D Value Sets: Inventory, Comparative Review and User Guide. Berlin: Springer Netherland, 2007.
171. Devlin N, Shah, K., Feng, Y., Mulhern, B. and Van Hout, B. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. OHE 2016;Office of Health Economics Research Paper 16/01.
172. Rodger AJ, Jolley D, Thompson SC, et al. The impact of diagnosis of hepatitis C virus on quality of life. Hepatology 1999;30:1299-301.
173. Fan SY, Eiser C, Ho MC. Health-related quality of life in patients with hepatocellular carcinoma: a systematic review. Clin Gastroenterol Hepatol 2010;8:559-64 e1-10.
174. Bownik H, Saab S. Health-related quality of life after liver transplantation for adult recipients. Liver Transpl 2009;15 Suppl 2:S42-9.
175. Ratcliffe J, Longworth L, Young T, et al. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. Liver Transpl 2002;8:263-70.
176. Vera-Llonch M, Martin M, Aggarwal J, 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;38:124-33.
177. NICE. Ledipasvir–sofosbuvir for treating chronic hepatitis C: Technology appraisal guidance [TA363], 2015.
178. Joint Formulary Committee. British National Formulary, 69, 2016.

179. Curtis L, Burns A. Unit Costs of health and Social Care. Personal Social Services Research Unit, 2016.
180. Thorlund K, Druyts E, El Khoury AC, et al. Budget impact analysis of boceprevir and telaprevir for the treatment of hepatitis C genotype 1 infection. Clinicoecon Outcomes Res 2012;4:349-59.
181. NICE. Clinical Guidance CG90: Depression in adults: recognition and management, 2009.
182. Curtis L. Unit Costs of health and Social Care. Personal Social Services Research Unit, 2013.
183. NICE. Hepatitis B (chronic): diagnosis and management (CG165). 2013.
184. Department of Health. Reference Costs 2015-16, 2016.
185. Backx M, Lewszuk A, White JR, et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. J Viral Hepat 2014;21:208-15.
186. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology 2001;34:809-16.
187. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. Semin Liver Dis 2000;20:17-35.
188. Seeff LB. The history of the "natural history" of hepatitis C (1968-2009). Liver Int 2009;29 Suppl 1:89-99.
189. Brady B, Siebert U, Sroczynski G, et al. Pegylated interferon combined with ribavirin for chronic hepatitis C virus infection: an economic evaluation [Technology Report no 82]. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2007.
190. Kiyosawa K, Sodeyama T, Tanaka E, et al. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibody to hepatitis C virus. Hepatology 1990;12:671-5.
191. Roudot-Thoraval F, Bastie A, Pawlotsky JM, et al. Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: a French survey of 6,664 patients. The Study Group for the Prevalence and the Epidemiology of Hepatitis C Virus. Hepatology 1997;26:485-90.
192. Tong MJ, el-Farra NS, Reikes AR, et al. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995;332:1463-6.
193. EMA. MAVIRET Summary of Product Characteristics DRAFT, 2017.
194. Muir A, Strasser S, Wang S, et al. 753 High SVR Rates With ABT-493 + ABT-530 Co-Administered for 8 Weeks in Non-Cirrhotic Patients with HCV Genotype 3 Infection. Gastroenterology;150:S1047.
195. Poordad F. FF, Wang S., Asatryan A., Hassanein T.I., Aguilar H., Lalezari J., Overcash J.S., Ng T., Lovell S.S., Lin C.-W., Kort J., Mensa F. High SVR rates with the combination of ABT-493 + ABT-530 for 8 weeks in non-cirrhotic patients with HCV genotype 1 or 2 infection. Gastroenterology 2016;150:S1046-S1047.
196. Hassanein T, Poordad F, Kwo P, et al. High SVR rates with ABT-493 + ABT-530 in non-cirrhotic patients with HCV genotypes 1, 2, 3 infection. APASL, 2016.
197. Gane E, Poordad F, Wang S, et al. High Efficacy of ABT-493 and ABT-530 Treatment in Patients With HCV Genotype 1 or 3 Infection and Compensated Cirrhosis. Gastroenterology 2016;151:651-659.e1.
198. Gane E, Poordad F, Asatryan A, et al. High efficacy and favorable safety of ABT-493 and ABT-530 co-administration for 12 weeks in HCV genotype 1-infected patients with cirrhosis (surveyor-i). Journal of Hepatology 2016;64:S757.
199. Welzel T. ZS, Dumas E.O., Asselah T., Shaw D., Hazzan R., Forns X., Matias T.P., Lu W., Cohen D.E., Feld J. GARNET: 98% SVR rates following eight-week treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir for patients with HCV genotype 1b infection without cirrhosis. Hepatology International 2017;11:S1002.
200. Arama V. LA, Catana R., Stratan L., Nastase R.M., Molagic V., Radulescu M., Munteanu D.I., Tiliscan C., Orfanu A., Duport I., Murariu C., Bodosca I., Nita V., Popescu C. The efficacy of OBV/PTV/r + DSV and RBV in a romanian cohort with genotype 1 HCV compensated cirrhosis. Hepatology International 2017;11:S1028-S1029.
201. Lawitz E, Sullivan G, Rodriguez-Torres M, et al. Exploratory trial of ombitasvir and ABT-450/r with or without ribavirin for HCV genotype 1, 2, and 3 infection. J Infect 2015;70:197-205.
202. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med 2014;370:222-32.

203. Dore GJ, Conway B, Luo Y, et al. Efficacy and safety of ombitasvir/paritaprevir/r and dasabuvir compared to IFN-containing regimens in genotype 1 HCV patients: The MALACHITE-I/II trials. J Hepatol 2016;64:19-28.
204. Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet 2015;385:1075-86.
205. Sperl J, Horvath G, Halota W, et al. Efficacy and safety of elbasvir/grazoprevir and sofosbuvir/pegylated interferon/ribavirin: A phase III randomized controlled trial. J Hepatol 2016;65:1112-1119.
206. Foster G, Agarwal K, Cramp M, et al. Elbasvir/grazoprevir plus sofosbuvir in treatment-naive and treatment-experienced cirrhotic patients with hepatitis C virus genotype 3 infection treated for 8, 12, or 16 weeks: final results of the C-ISLE study. . EASL. Amsterdam, the Netherlands, 2017.
207. Gane EJ, Hyland RH, An D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. Gastroenterology 2015;149:1454-1461.e1.
208. Gane EJ, Stedman CA, Hyland RH, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology 2014;146:736-743.e1.
209. Bourliere M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis 2015;15:397-404.
210. Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. Lancet Infect Dis 2015;15:1049-54.
211. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N Engl J Med 2015;373:2618-28.
212. Pianko S, Flamm SL, Shiffman ML, et al. Sofosbuvir Plus Velpatasvir Combination Therapy for Treatment-Experienced Patients With Genotype 1 or 3 Hepatitis C Virus Infection: A Randomized Trial. Ann Intern Med 2015;163:809-17.
213. Everson GT, Towner WJ, Davis MN, et al. Sofosbuvir With Velpatasvir in Treatment-Naive Noncirrhotic Patients With Genotype 1 to 6 Hepatitis C Virus Infection: A Randomized Trial. Ann Intern Med 2015;163:818-26.
214. Wehmeyer MH, Jordan S, Luth S, et al. Efficacy and safety of sofosbuvir-based triple therapy in hepatitis C genotype 4 infection. Dig Liver Dis 2015;47:811-4.
215. Lawitz E, Poordad F, Brainard DM, et al. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. Hepatology 2015;61:769-75.
216. Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2014;383:515-23.
217. Rodriguez-Torres M, Lawitz E, Kowdley KV, et al. Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naive patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial. J Hepatol 2013;58:663-8.
218. Leroy V, Angus P, Bronowicki JP, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). Hepatology 2016;63:1430-41.
219. Hezode C, Leroy V, Rosa I, et al. Efficacy and safety of sofosbuvir and daclatasvir for 8 weeks in treatment-naïve non-cirrhotic patients with chronic hepatitis C virus genotype 3 infection. . EASL. Amsterdam, the Netherlands, 2017.
220. Buti M, Calleja JL, Lens S, et al. Simeprevir in combination with sofosbuvir in treatment-naive and -experienced patients with hepatitis C virus genotype 4 infection: a Phase III, open-label, single-arm study (PLUTO). Aliment Pharmacol Ther 2017;45:468-475.

221. Pearlman BL, Ehleben C, Perrys M. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related Child's class A cirrhosis. Gastroenterology 2015;148:762-70.e2; quiz e11-2.
222. Lawitz E, Matusow G, DeJesus E, et al. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: A phase 3 study (OPTIMIST-2). Hepatology 2016;64:360-9.
223. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet 2014;384:1756-65.
224. Pol S, Ghalib RH, Rustgi VK, et al. Daclatasvir for previously untreated chronic hepatitis C genotype-1 infection: a randomised, parallel-group, double-blind, placebo-controlled, dose-finding, phase 2a trial. Lancet Infect Dis 2012;12:671-7.
225. Rodriguez-Torres M, Lawitz E, Yangco B, et al. Daclatasvir and Peginterferon/Ribavirin for Black/African-American and Latino Patients with HCV infection. Ann Hepatol 2016;15:834-845.
226. Hezode C, Hirschfield GM, Ghesquiere W, et al. Daclatasvir plus peginterferon alfa and ribavirin for treatment-naive chronic hepatitis C genotype 1 or 4 infection: a randomised study. Gut 2015;64:948-56.
227. Hezode C, Alric L, Brown A, et al. Randomized controlled trial of the NS5A inhibitor daclatasvir plus pegylated interferon and ribavirin for HCV genotype-4 (COMMAND-4). Antivir Ther 2015;21:195-205.
228. Dore GJ, Lawitz E, Hezode C, et al. Daclatasvir plus peginterferon and ribavirin is noninferior to peginterferon and ribavirin alone, and reduces the duration of treatment for HCV genotype 2 or 3 infection. Gastroenterology 2015;148:355-366.e1.
229. Zeuzem S, Hezode C, Bronowicki JP, et al. Daclatasvir plus simeprevir with or without ribavirin for the treatment of chronic hepatitis C virus genotype 1 infection. J Hepatol 2016;64:292-300.
230. Hezode C, Almasio PL, Bourgeois S, et al. Simeprevir and daclatasvir for 12 or 24 weeks in treatment-naive patients with hepatitis C virus genotype 1b and advanced liver disease. Liver Int 2017.
231. Lagging M, Brown A, Mantry PS, et al. Grazoprevir plus peginterferon and ribavirin in treatment-naive patients with hepatitis C virus genotype 1 infection: a randomized trial. J Viral Hepat 2016;23:80-8.
232. Manns MP, Vierling JM, Bacon BR, et al. The combination of MK-5172, peginterferon, and ribavirin is effective in treatment-naive patients with hepatitis C virus genotype 1 infection without cirrhosis. Gastroenterology 2014;147:366-76.e6.
233. Poordad F, Lawitz E, Kowdley KV, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med 2013;368:45-53.
234. Jacobson IM, Dore GJ, Foster GR, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2014;384:403-13.
235. Manns M, Marcellin P, Poordad F, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2014;384:414-26.
236. Moreno C, Hezode C, Marcellin P, et al. Efficacy and safety of simeprevir with PegIFN/ribavirin in naive or experienced patients infected with chronic HCV genotype 4. J Hepatol 2015;62:1047-55.
237. Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. Hepatology 2013;58:1918-29.
238. Manns M, Reesink H, Berg T, et al. Rapid viral response of once-daily TMC435 plus pegylated interferon/ribavirin in hepatitis C genotype-1 patients: a randomized trial. Antivir Ther 2011;16:1021-33.
239. Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology 2014;146:430-41.e6.

240. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. Gastroenterology 2014;146:1669-79.e3.
241. Jensen D, Sherman KE, Hezode C, et al. Daclatasvir and asunaprevir plus peginterferon alfa and ribavirin in HCV genotype 1 or 4 non-responders. J Hepatol 2015;63:30-7.
242. Everson GT, Sims KD, Rodriguez-Torres M, et al. Efficacy of an interferon- and ribavirin-free regimen of daclatasvir, asunaprevir, and BMS-791325 in treatment-naive patients with HCV genotype 1 infection. Gastroenterology 2014;146:420-9.
243. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377-84.
244. Rabin R, Oemar M, Oppe M, et al. EQ-5D-5L user guide: basic information on how to use the EQ-5D-5L instrument, Version 1.0. Rotterdam, the Netherlands: EuroQol Group, 2011.
245. Ware J, Kosinoski M, Bjorner J, et al. User's manual for the SF-36v2 health survey. 2nd ed. Lincoln, RI: QualityMetric Incorporated, 2007.
246. Szende A, Williams A. Measuring self-reported population health: an international perspective based on EQ-5D. EuroQol Group Monographs Volume 1. SpringMed Publishing, 2004.
247. Khanna D, Singal A, Kalra OP. Comparison of cutaneous manifestations in chronic kidney disease with or without dialysis. Postgrad Med J 2010;86:641-7.
248. Min JW, Kim SH, Kim YO, et al. Comparison of uremic pruritus between patients undergoing hemodialysis and peritoneal dialysis. Kidney Res Clin Pract 2016;35:107-13.
249. Cure S, Guerra I, Dusheiko G. Cost-effectiveness of sofosbuvir for the treatment of chronic hepatitis C-infected patients. J Viral Hepat 2015;22:882-9.
250. McEwan P, Bennett H, Ward T, et al. The cost-effectiveness of daclatasvir-based regimens for the treatment of hepatitis C virus genotypes 1 and 4 in the UK. Eur J Gastroenterol Hepatol 2016;28:173-80.
251. McEwan P, Ward T, Webster S, et al. Modeling The Cost-Effectiveness of The All Oral, Direct-Acting Antiviral Regimen Daclatasvir Plus Sofosbuvir In Patients Co-Infected With Hepatitis C Virus (HCV) And HIV. Value Health 2015;18:A628.
252. McEwan P, Selvapatt N, Brown A, et al. A clinician's guide to the cost and health benefits of hepatitis C cure assessed from the individual patient perspective. Eur J Gastroenterol Hepatol 2017;29:208-214.
253. Faria R, Woods B, Griffin S, et al. Prevention of progression to cirrhosis in hepatitis C with fibrosis: effectiveness and cost effectiveness of sequential therapy with new direct-acting anti-virals. Aliment Pharmacol Ther 2016;44:866-76.
254. Connoly M, Kotsopoulos N. Assessing the long-term fiscal consequences attributed to Hepatitis C and the impact of ledipasvir / sofosbuvir combination curative therapies in UK. Hepatology 2016;64:53.
255. Selvapatt N, Ward T, Ananthavarathan A, et al. Cost-Effectiveness of Birth Cohort Screening and Treatment for HCV in the UK: An Exploratory Analysis. Journal of Hepatology;64:S465.
256. Thokala P, Simpson EL, Tappenden P, et al. Ledipasvir-Sofosbuvir for Treating Chronic Hepatitis C: A NICE Single Technology Appraisal-An Evidence Review Group Perspective. Pharmacoeconomics 2016;34:741-50.
257. Westerhout KY, Treur M, Mehnert A, et al. Cost-Utility Analysis of Simeprevir With Peginterferon + Ribavirin (SMV/PR) in the Management of Genotype 1 (G1) and 4 (G4) Hepatitis C Virus (HCV) Infection; from the Perspective of the Uk National Health Service (NHS). Value Health 2014;17:A679.
258. Bjornsson E, Verbaan H, Oksanen A, et al. Health-related quality of life in patients with different stages of liver disease induced by hepatitis C. Scand J Gastroenterol 2009;44:878-87.
259. Chong CA, Gulamhussein A, Heathcote EJ, et al. Health-state utilities and quality of life in hepatitis C patients. Am J Gastroenterol 2003;98:630-8.
260. Custer B, Vahidnia F, Kessler D. Health-related quality of life in US blood donors with and without viral infections. 107 2014;97.
261. DeVecchis Wygant G, Mo L, Treitel M, et al. EQ-5D results in Asian patients with HCV G1b receiving DCV + ASV who are IFN intolerant/ineligibile. Abstracts of the 25th Annual Conference of APASL, February 20–24, 2016, Tokyo, Japan. Hepatology International 2016;10:142.

262. Kaishima T, Akita T, Aikata H, et al. Cost-effectiveness analysis related to HCV treatment is possible to be estimated in each province. Abstracts of the 25th Annual Conference of APASL, February 20–24, 2016, Tokyo, Japan. Hepatology International 2016;10:S148-9.
263. McDonald SA, Hutchinson SJ, Palmateer NE, et al. Decrease in health-related quality of life associated with awareness of hepatitis C virus infection among people who inject drugs in Scotland. J Hepatol 2013;58:460-6.
264. Nouvertne D, Perry R, Milligan G. P24: Health-Related Quality of Life and productivity impairment in chronic hepatitis C patients in Germany. Journal of Viral Hepatitis 2014;21:34-35.
265. Nwankwo C, Sung AH, Pike J. Self-Reported Health Related Quality Of Life Of Hepatitis C Virus (Hcv) Genotype 1 Patients With And Without Comorbid Conditions. Value in Health 2014;17:A369-A370.
266. Pol S, Chevalier J, Branchoux S, et al. P0747 : Health related quality of life and utility values in chronic hepatitis C patients: A cross-sectional study in France, the UK and Germany. Journal of Hepatology 2015;62:S606.
267. Samp JC, Perry R, Piercy J, et al. Patient health utility, work productivity, and lifestyle impairment in chronic hepatitis C patients in France. Clin Res Hepatol Gastroenterol 2015;39:307-14.
268. Samp JC, Perry R, Piercy J, et al. Utility Values Of Hepatitis C Patients In France: Results By Liver Disease Stage And Treatment Outcome. Value in Health 2014;17:A279.
269. Scalone L, Ciampichini R, Fagiuoli S, et al. Comparing the performance of the standard EQ-5D 3L with the new version EQ-5D 5L in patients with chronic hepatic diseases. Qual Life Res 2013;22:1707-16.
270. Schafer A, Wittchen HU, Backmund M, et al. Psychopathological changes and quality of life in hepatitis C virus-infected, opioid-dependent patients during maintenance therapy. Addiction 2009;104:630-40.
271. Schwarzinger M, Cossais S, Deuffic-Burban S, et al. P0745 : EQ-5D utility index in French patients with chronic hepatits C (CHC) infection: severe comorbidities and perceived progression of CHC infection matter more than actual liver disease stage. Journal of Hepatology 2015;62:S605.
272. Scott J, Rosa K, Fu M, et al. Fatigue during treatment for hepatitis C virus: results of self-reported fatigue severity in two Phase IIb studies of simeprevir treatment in patients with hepatitis C virus genotype 1 infection. BMC Infect Dis 2014;14:465.
273. Younossi ZM, Stepanova M, Cure S, et al. P718 Estimating health status using EQ5D for chronic hepatitis C (CHC) patients treated with sofosbuvir (SOF) containing regimens. Journal of Hepatology 2014;60:S308.
274. Vargas CL, Espinoza MA, Giglio A, et al. Cost Effectiveness of Daclatasvir/Asunaprevir Versus Peginterferon/Ribavirin and Protease Inhibitors for the Treatment of Hepatitis C Genotype 1b Naive Patients in Chile. PLoS One 2015;10:e0141660.
275. Longworth L, Young T, Ratcliffe J, et al. Economic evaluation of the Transplantation Programme in England and Wales: an assessment of the costs of liver transplantation. Report to the Department of Health. 2001.
276. Yeung MW, Young J, Moodie E, et al. Changes in quality of life, healthcare use, and substance use in HIV/hepatitis C coinfected patients after hepatitis C therapy: a prospective cohort study. HIV Clin Trials 2015;16:100-10.
277. Huang R, Rao H, Wei L. Assessment of health-related quality of lige and related factors in Chinese patients with chronic hepatitis C virus infection. Abstracts of the 26th Annual Conference of APASL, February 15–19, 2017, Shanghai, China. Hepatology International 2017;11:S558.
278. Wygant G, Mo L, Treitel M, et al. Patient reported outcomes in IFN/ribavirin intolerant/ineligible Asian patients from Mainland China receiving daclatasvir + asunaprevir for the treatment of HCV genotype 1b infection. Abstracts of the 26th Annual Conference of APASL, February 15–19, 2017, Shanghai, China. Hepatology International 2017;11:S1001-1002.
279. Cheng W, Sobhonslidsuk A, Pham TTT, et al. Impact of a 12-week oral regimen of elbasvir/grazoprevir (EBR/ GZR) on health-related quality of life (HRQOL) and fatigue in treatment-naive patients with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, or 6 infection: Data from the C-CORAL study. Abstracts of the 26th Annual Conference of APASL, February 15–19, 2017, Shanghai, China. Hepatology International 2017;11:S298-S299.

280. Gschwantler M, Ferenci P, Bauer BJ, et al. 928 Burden of disease in patients with chronic hepatitis C in the Austrian REAL Study. Hepatology 2016;64:466A.
281. Akpo E, Sbarigia U, Kleintjens J. P10: Factors associated with medical resource utilisation and related costs in treatment experienced patients with genotype 1 chronic hepatitis C. Journal of Viral Hepatitis 2014;21:26-27.
282. Akpo EI, Sbarigia U, Wan G, et al. Determinant Factors of the Direct Medical Costs Associated with Genotype 1 Hepatitis C Infection in Treatment-Experienced Patients. Drugs R D 2015;15:335-49.
283. Akpo EI, Cerri K, Kleintjens J. Predicting the impact of adverse events and treatment duration on medical resource utilization-related costs in hepatitis C genotype 1 treatment-naive patients receiving antiviral therapy. Pharmacoeconomics 2015;33:409-22.
284. Barclay S, Cooke G, Irving W, et al. PTU-105 Real world effectiveness, safety and cost per cure in hepatitis C patients treated with protease inibitor based therapy: results from the HCV research UK cohort. Gut 2015;64:A107-A108.
285. Barnabas A, Trueman D, Goad C. Costs associated with adverse events in the treatment of hepatitis C virus infection with protease inhibitor triple therapy in a specialist UK centre. 23rd Annual Conference of APASL March 12–15, 2014, Brisbane, Australia. Hepatology International 2014;8:S224.
286. Dibonaventura MD, Yuan Y, Lescrauwaet B, et al. Multicountry burden of chronic hepatitis C viral infection among those aware of their diagnosis: a patient survey. PLoS One 2014;9:e86070.
287. NICE. Sofosbuvir for treating chronic hepatitis C: Technology appraisal guidance [TA330], 2014.
288. Innes HA, Hutchinson SJ, Allen S, et al. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. Hepatology 2011;54:1547-58.
289. Orkin C, Leach E, Flanagan S, et al. High prevalence of hepatitis C (HCV) in the emergency department (ED) of a London hospital: should we be screening for HCV in ED attendees? Epidemiol Infect 2015;143:2837-40.
290. Sewell J, Capocci S, Johnson J, et al. Expanded blood borne virus testing in a tuberculosis clinic. A cost and yield analysis. J Infect 2015;70:317-23.
291. Verma S, Foster GR, Irving W, et al. Health resource usage in peri-transplant patients during 12 weeks of therapy with sofosbuvir (SOF), with or without ribavirin (RBV) and an NS5A inhibitor. Hepatology 2015;62:789A-790A.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Glecaprevir with pibrentasvir for treating chronic hepatitis C [ID1085]

Dear Dominic,

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 26 July 2017 from AbbVie. 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 **Friday 1 September 2017**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Victoria Kelly, Technical Lead (Victoria.Kelly@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

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Literature searching

A1. **Priority question**: Please clarify the syntax used in the Embase search for clinical evidence (Appendix D of the company submission, page 11-12, line 69). The ERG is concerned that the Boolean logic is incorrect and that results have been limited to "clinical trial" in the title/abstract only. The number of records retrieved appears to be low compared to the results retrieved in other databases.

A2. **Priority question**: Please explain why all searches in Appendix G of the company submission do not include the following interventions specified in the decision problem: paritaprevir, ribavirin, alfa 2a peginterferon and peginterferon alpha2b.

A3. **Priority question**: Please clarify the syntax used for the Embase searches Appendices G, H and I of the company submission. It appears that parentheses are missing from the search strategies resulting in unusually low results in comparison to PubMed searches. The ERG is unable to replicate the searches in their current form. Please provide a search strategy that can be replicated.

A4. **Priority question**: Please provide full search strategies and number of records retrieved for EconLit and the Tufts CE Registry searches listed as sources in Appendices G, H and I of the company submission.

A5. Please provide URLs, full search strategies and number of records retrieved for the conference proceedings reported in Appendices D, G, H and I. The ERG notes that 549 conferences proceedings have been included in the PRISMA flow diagram for clinical SLR (Appendix D of the company submission, page 15).

A6. Please explain why the term "hepacivirus" was not included as a MeSH term in the PubMed or Cochrane Library searches or as a free text term in PubMed, Embase or Cochrane Library searches.

A7. Please provide full details of the results of the Cochrane Library searches (i.e. result numbers from the individual databases).

A8. Please justify the use of a trials filter in the Cochrane Library searches for clinical evidence (Appendix D, page 12-13) given that the Cochrane Library is a study design specific resource.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A9. Please clarify why the Embase strategy for clinical evidence (Appendix D, Page 12, line 69) was limited to remove conference abstracts and papers.

A10. Please clarify how the number of Embase records reported in the PRISMA diagram for the cost effectiveness systematic literature review (Appendix G, page 174) was retrieved. The corresponding search strategy (Appendix G page 170) shows 1125557 records as the last search results retrieved.

A11. Please explain the use of a cost filter in the NHS EED database (Appendix G, page 172 of the company submission). This resource is already filtered for cost studies.

A12. Please clarify if the syntax "â€" used in the PubMed searches (Appendix G, page 171, line 7 and Appendix I, page 298, line 38) is a typographical error or if this is how the strategy was run.

A13. Please check whether "?" has been used incorrectly in PubMed searches in CS Appendix G, page 171, line 6 and CS Appendix I, page 298, line 30. Please also check if "*" has also been used incorrectly in CS Appendix H, page 260, line 9. The NLM PubMed database does not support the use of "?" or "*" as a wildcard for character substitution. Please examine if potentially relevant references have been missed as a consequence.

A14. Please explain the use of the Boolean 'NOT' in the Embase Health-related quality-of-life search (Appendix H, page 259-60, line 23). This appears to exclude all articles which contain the terms "eq-5d", "eq5d" or "euroqol".

A15. Please explain the final set of results for the Health-related quality-of-life Cochrane Library search in Appendix H, page 261, line 20 which appears to limit the results to EQ-5D.

A16. Please explain the final set of results for the Cost and healthcare resource Cochrane Library searches (Appendix I page 300) which has been limited to "hepatitis C" or "HCV" in the abstract only. The ERG is concerned that a number of relevant references may have been missed with this limit.

A17. Please clarify why a UK filter was applied to Cost and healthcare resource identification, measurement and valuation searches (Appendix I).

A18. Please explain why the search terms "China", "Asia", "Japan", "Latin", "HIV", "guidelines", "acute", "pcr", "assay"," hepatitis b" and "IL-28" have been included in the PubMed searches for Cost and healthcare resource identification, measurement and valuation (Appendix I, page 298, line 47) but have not been included in the associated Embase and Cochrane Library searches.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A19. All literature reviews conducted in the clinical effectiveness and cost-effectiveness section were conducted as an update of the systematic literature review (SLR) conducted in TA430. This approach is based on a full reliance on the SLR results in TA430, not only in terms of search strategy but also the review process and reviewers. Please ensure that the search strategy of the submission in TA430 is in line with the search strategy of this submission and that no relevant studies that might have been interesting for this appraisal were missed or excluded in TA430.

Included and excluded studies

A20. A. Please provide the definition of chronically infected used in the systematic review (Table 121, p14 of the appendices).

B. Please clarify why studies of patients with renal transplant or HCV-HIV co-infected patients were excluded from the review (Table 121 p14 of the appendices), given that they were included in the NICE final scope.

A21. Please clarify why subgroup analyses was not undertaken in patients stratified by previous treatment response (non-response, partial response, relapsed), as specified in the NICE final scope. There appears to be evidence to support clinical outcomes in this population (specifically from ENDURANCE-1, -2 and -4, and EXPEDITION-1 trials).

A22. For EXPEDITION-2, EXPEDITION-4, MAGELLAN-I and MAGELLAN-II, consider the following:

- Please clarify how these studies were identified. Section B.2.2, page 36 of the company submission states that these studies were not found in the systematic review.
- Were any other relevant trials identified which were not found in the systematic review (particularly studies in specific populations)?
- The company submission states that 'limited information is presented for EXPEDITION-2 and MAGELLAN-II as these trials have only recently been completed. 'Please clarify when a full publication will be available for EXPEDITION-2?
- Reference 43 of the submission relating to MAGELLAN-II is missing (Reau N, Kwo P, Rhee S, et al. MAGELLAN-2: safety and efficacy of glecaprevir-pibrentasvir in liver or renal transplant adults with chronic hepatitis C genotype 1-6 infection. EASL. Amsterdam, the Netherlands, 2017.). Please supply the reference.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A23. Please provide bibliographical details of the 66 studies excluded at full paper stage in the systematic review and the reasons for exclusion (Figure 17, Appendix, page 15).

Clinical Effectiveness

Glecaprevir-pibrentasvir studies

A24. Please clarify the following discrepancies:

- Table 65, page 158 of the company submission show the SVR12 rate to be [redacted] for G/P in GT1/TN/NC; but on page 108, the SVR12 is [redacted] from ENDURANCE-1 and 96.6% (28/29) from SURVEYOR-I. The combined SVR12 rate should therefore be [redacted]

- Table 66, page 161 of the company submission show the SVR12 rate to be [redacted] for G/P in GT1/TE/NC; but on page 108, the SVR12 is [redacted] from ENDURANCE-1 and 100% (5/5) from SURVEYOR-I. Therefore the combined figure should be: [redacted]

A25. Please clarify whether patients were randomised to all three treatment groups or just to the two 12 week groups in Endurance-3. If patients were not randomised to the 8 week group please explain why the 8 week G/P arm was included in the trial and why it was not part of the randomised comparison.

A26. Please provide SVR12 rates for the placebo arm of ENDURANCE-2 and the SVR12 rates for the placebo arms of other AbbVie trials, where available, given that spontaneous remissions of chronic HCV infection is possible.

Comparator studies

A27. Please explain why results from the following studies were not included in the review:
- C-SURFER - NCT02092350
- C-EDGE CO-STAR - NCT02105688
- C-SCAPE, NCT01932762
- C-EDGE CO-INFECTION, NCT02105662
- ADVANCE, NCT00627926
- ALLY-2, NCT02032888
- COMMAND-4, AI444042
- LONESTAR, NCT01726517
- NCT01975675
- NCT02168361
- PILLAR, NCT00882908
- PROMISE, NCT01281839
- QUEST-1, NCT01289782
- QUEST-2, NCT01290679
- ERADICATE, NCT01878799

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

- RESTORE, NCT01567735
- SYNERGY, NCT01805882
- NCT02021656
- NCT01565889
- ELECTRON-2

A28. **Priority question**: For each SVR rate presented for each comparator in tables 65 and 66 (pages 157 – 160), please explain whether any other data were available, and if so, why this rate was selected. If rates from multiple studies were pooled, please explain how they were pooled and provide the calculations with data from each study separately.

A29. **Priority question**: For each adverse event presented for each comparator in tables 67 and 68 (pages 163 – 164), please explain whether any other data were available, and if so, why this rate was selected. If rates from multiple studies were pooled, please explain how they were pooled and provide the calculations with data from each study separately.

A30. In Table 59 (page 148 -149), genotype 2 is split for 'Comparators for IFN-eligible patients' and 'Comparators for IFN-ineligible patients'; but Tables 65 and 66 (pages 158 – 163) do not report separate results for these two groups. Please clarify whether the same result for SOF/VEL was used.

A31. A. Please clarify how SVR12 is estimated to be 77.3% for SOF+RBV in GT2/TE/CC in Table 66 (page 161 of the company submission). The reference states: "Pooled data from FUSION (Sovaldi SmPC),[150] VALENCE (Sovaldi SmPC)[150] and ASTRAL-2 (TA43)[1]". However, according to Table 130 (Appendix D.1.1.4, page 60) SVR12 rates for these three studies are 100%, 93% and 94%, respectively. If the raw data from the individual studies are reported in the company submission, please explain where; if not, please provide them in all instances where data are pooled.

B. Please clarify how how SVR12 is estimated to be 96.8% (184/190) for SOF + DCV in Table 65 (, page 159 of the company submission). According to the reference it is "Pooled data from ENDURANCE-3 ITT population[52, 88] and ALLY-3[155]". However, according to Table Table 130 (Appendix D.1.1.4, page 60) SVR12 rates for SOF + DCV are 99% (N=101) for ALLY-3 (i.e. 100/101) and according to Table 31 (CS, page 112) 96.5% (111/115) for ENDURANCE-3. The pooled result would then be: 211/216 = 97.7%.

Indirect comparisons (section B.2.10 of the company submission)

A32. **Priority question**: The company states that naïve indirect comparisons were used to compare effectiveness of interventions. However, no results of these naïve indirect comparisons are reported. Please provide the results for each comparison in each

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

population. And please complete section B.2.10.1 (Uncertainties in the indirect and mixed treatment comparisons).

A33. The following comparators were included in the NICE scope but excluded from the company submission on the basis that they are not used in current NHS practice (Table 1, page 20). Please reconsider whether it is appropriate to include these comparators or provide evidence to support the case for excluding them from the clinical and cost effectiveness review.

- Daclatasvir in combination with sofosbuvir, with or without ribavirin (for specific people with genotype 1, or 4; as recommended by NICE)
- Peginterferon alfa with ribavirin (for genotypes 1– 6). The committee in TA430 concluded that PR is a relevant comparator across all subgroups. Excluding this comparator suggests the evidence presented is for interferon ineligible patients only.
- Sofosbuvir in combination with ribavirin, with or without peginterferon alfa (for specific people with genotypes 1–6; as recommended by NICE).

Ongoing studies

A34. Ongoing studies are listed in section B2.12 , page 135 of the company submission

- Please clarify whether further details are currently available from these studies.
- Please provide timelines and dates for when the results from these studies will be available.
- Please also clarify whether further analyses are planned for any of the glecaprevir-pibrentasvir trials included in the company submission.

Section B: Clarification on cost-effectiveness data

Patient population

B1. In the company submission, GT1 patients are not divided into GT1a and GT1b subgroups because of the same treatment duration and similarity of treatment response for the glecaprevir-pibrentasvir GT1a and GT1b subgroups. However, in some NICE technology appraisals there were differences in clinical effectiveness for comparator technologies (for example in TA413) by GT1a and GT1b subgroup, which would result in differential comparative effectiveness. Therefore, consider exploring analyses for GT1a and GT1b subgroups or provide justification why this may not be appropriate.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

B2. Baseline patient population characteristics were presented in Tables 61 and 62 on page 151 of the company submission. Please clarify whether these characteristics are the same for all genotypes.

B3. The subgroups listed below were included in the NICE final scope. Please reconsider whether it would be useful to provide cost effectiveness analysis for these subgroups or provide further justification why this may not be appropriate (other than these analyses were not provided in previous hepatitis C submissions.

- Co-infection with HIV (in TA430 it was discussed that disease progression might be faster)
- Previous treatment received (with DAA or without DAA)
- People who have received treatment before liver transplantation
- Response to previous treatment
- With and without renal impairment
- Ineligible/intolerant for interferon treatment (not only for GT2)

Model structure

B4. **Priority question:** Please consider the following issues and incorporate each of the suggested changes individually and simultaneously in exploratory scenario analyses. Please provide the results for all subgroups (also please provide the new model with the functionality of conducting these suggested exploratory analyses).

- In the company submission report, it is not clear whether patients were allowed to die or to transit to more advanced disease stages during the on-treatment period.

    i. Please clarify the underlying assumptions and confirm that background mortality was incorporated during the on-treatment period in the company base-case.

    ii. If not already incorporated, please explore the impact of disease progression during the on-treatment period as well.

- There have been reports of spontaneous remissions of chronic HCV infection in ~3% to 10% of individuals (Thomas et al 2000, JAMA; Watanabe et al 2003, J Med Virol).[1, 2] Please incorporate the impact of spontaneous remission (i.e. a positive transition probability from F0 HCV to no HCV in the economic model)

- In low-risk patients, there is clear evidence of late relapse occurring post-SVR, together with published estimated rates of late relapse (e.g. Simmons et al 2016, Clin Infect Dis; Klag et al 2017, J Hepatol).[3, 4] Please incorporate the reactivation of disease in the economic model, in such a way that a patient

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

who achieved SVR, should return back to his/her pre-SVR fibrosis stage after the disease reactivation.

- Please provide a qualitative impact analysis of incorporating onward transmission (with and without re-infection) in the model by explaining the expected model outcomes step by step.

Clinical Inputs (disease progression)

B5. **Priority question**: If questions A28, A29, A32 and A33 lead to any updates of the data (e.g. by including other available non-randomized observational clinical studies), please provide an updated model including these data and provide all new results.

B6. There are some minor inconsistencies between the datasets used for SVR rates and AE rates, for example in Table 65 on page 158, for GT3 TN NC SOF/VEL SVR is taken from ASTRAL-3, but in Table 68, the AE rate for the same subgroup was from pooled data from ASTRAL-3 and POLARIS-3 studies. Please check and confirm that the same datasets were used for deriving SVR rates and AE rates; if there are exceptions, either explain the reason or alter the input to achieve consistency.

B7. The costs of five adverse events were incorporated into the economic model (anaemia, rash depression, grade ¾ neutropenia and depression). Please provide further clarification of the criteria for selecting adverse events in the economic model.

B8. The expected treatment duration calculation appears to be based on an assumption that patients discontinue treatment at the midpoint of the licensed treatment duration.

- Please provide the median time to treatment discontinuation for all treatments for each subgroup

- Please provide the results of the scenario analysis (as facilitated by the dropdown box on sheet 'main model input' cell H38) in which it is assumed that each treatment was administered during the whole licensed treatment duration.

B9. For the Fibrosis progression, please use the alternative transition probabilities from Grischenko et al 2009 (together with Kanwal HRs for GTs) instead of Thien 2009 in a scenario analysis (as in TA413).

B10. Some of the transition probabilities in Table 75, page 178 are different from those used in TA430. .

- For CC to DCC, CC to HCC and DCC to HCC: please justify the choice of Fattovich et al 1997 as the input source, and conduct a scenario analysis using the input from Cardoso et al 2010.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

- For LT related death probabilities: please justify the model input used and provide a scenario analysis using the inputs from TA430 (EAP data and Bennet et al.)

Utility

B11. Please provide the results of the following scenario analyses (with functionalities in the model) individually and simultaneously.

- Incorporating the age based utility decrement (using a similar approach to TA413)
- Assume no utility gain from SVR
- Assuming no treatment related health utility change (also can you please confirm the consistency between the datasets used in Table 78 with the datasets used to derive SVR and AE rates?)
- Applying health related disutilities for AEs (for depression please do not forget that it might have impacts in later years).

Costs

B12. **Priority question**: It is stated in the company submission that the drug costs are charged daily. However an opened package may not be used. Please provide a scenario in which full costs of an opened package is incurred, even if the whole package was not consumed.

B13. Please provide a scenario analysis in which the inflation adjusted health state costs from TA430 (in Table 82) are used.

Cost effectiveness results

B14. **Priority question**: The results as presented in the company submission (document B) appear not to match the base case results found in the electronic model. Please explain if certain settings in the model should be changed in order to reproduce the results in B.3.7 or if the results in B.3.7 are not based on the submitted electronic model.

B15. The first scenario analysis (as described in section B.3.8.3) appears not to be fully implemented in the economic model. Instead, only step two of the changes made ([redacted]) appears to be implemented in a macro. Please confirm that step 1 and 3, i.e. changes in the [redacted] and the price for OBV/PTV/RTV ± DSV need to be implemented manually.
If this is indeed the case, please provide an updated macro that makes these changes automatically when running the macro.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

B16. Please include the parameter ‘treatment monitoring costs’ in both the PSA and the DSA.

Model validation

B17. Please provide the list of technical /internal validation tests conducted (section B.3.10.1 of the company submission).

B18. **Priority question**: Please consider conducting a cross-validation of the results for each sub-group by comparing the total life years, quality adjusted life years and costs for each comparator in the model with those in the models for previous assessments (e.g. TA430 and TA413).

B19. Please provide a scenario analysis using all inputs and assumptions in line with the TA430. Provide the results of glecaprevir-pibrentasvir and compare the LY, QALY and cost results of PR, BSC and SOF/VEL with the reported results in TA430.

References

[1] Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000;284(4):450-6.

[2] Watanabe H, Saito T, Shinzawa H, Okumoto K, Hattori E, Adachi T, et al. Spontaneous elimination of serum hepatitis C virus (HCV) RNA in chronic HCV carriers: a population-based cohort study. *J Med Virol* 2003;71(1):56-61.

[3] Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: a systematic review and meta-analysis. *Clin Infect Dis* 2016;62(6):683-94.

[4] Klag T, Dietz J, Werner CR, Schwarz JM, Lauer UM, Beck R, et al. Hepatitis C "true" late relapse beyond 48 weeks of sustained virologic response after direct acting antiviral therapy. *J Hepatol* 2017;66(4):862-3.

AbbVie Ltd
AbbVie House
Vanwall Business Park
Maidenhead
SL6 4UB

Helen Knight
Level 1A City Tower
Manchester
M1 4BT

1st September 2017

Dear [redacted],

Glecaprevir with pibrentasvir (G/P) (Maviret) for treating HCV [ID1085] – Response to Clarification Questions

Thank you for reviewing AbbVie's submission for the above appraisal and for acknowledging that the submission was clear and well-presented. We welcome the opportunity to provide further clarity on the clinical and cost-effectiveness data and are fully committed to providing a comprehensive response: please see our responses to the clarification questions below (after this letter). Appendices are attached as a separate document.

At the outset, we would like to draw your attention to a number of points, which are relevant to the decision making context and should thus be brought to the attention of the appraisal committee.

Firstly, AbbVie was awarded the tender contract (for Maviret) with NHS England for all regions and has now entered into a framework agreement, which will become effective on the 1st of September 2017. The implication is two-fold:

(i) The confidential pricing agreement with the Commercial Medicines Unit (CMU) described in the submission and presented in the economic model has been accepted. Please note that it was previously agreed that the comparator drug prices used for this economic analysis would be historical drug prices (PAS, discounted or list) used to gain a positive recommendation at the time of appraisal.

(ii) NHS England considered there was sufficient evidence of clinical benefit and cost saving for NHS England to exercise its discretion and to commission access to Maviret from the 1st of September across England, in advance of NICE publishing its technology appraisal.

Of note is that a number of the clarification questions request scenario analyses, which may no longer be relevant for decision making given that the confidential agreement offers a [redacted] So for example, question B12, which asks for a scenario in which full costs of an opened package is incurred may no longer be relevant for decision making as [redacted]

Secondly, we would like to refer to the decision problem meeting between AbbVie, NICE and the ERG which took place on the 6th of June 2017. At that meeting all parties appeared to accept collectively that a pragmatic approach to the health economic analysis is needed, largely owing to the complexity of the disease area, the vast number of sub-groups and the very large number of scenarios, which could potentially be modelled but which are unlikely to aid decision making. We trust you would agree that considering the complex HCV landscape, the focus of all parties should be to present analyses which help to inform decision making and that for consistency with previous appraisals in this field, there should be an alignment with recent submissions in HCV such as TA413 and TA430.

In conclusion, we have responded to all clarification questions and our response includes material facts, which we hope will help to frame the questions in the broader decision making context for the benefit of the appraisal

committee. Finally, we have increased flexibility in the economic model to enable the ERG to run further scenario analyses should they choose to do so.

Thank you for your time and please do not hesitate to contact me using the details below if you would like to discuss further.

Yours sincerely,

[redacted]

[redacted]
PHONE [redacted]
EMAIL [redacted]

Contents

	AbbVie Response to Clarification Questions
A1	**Priority question**: Please clarify the syntax used in the Embase search for clinical evidence (Appendix D of the company submission, page 11-12, line 69). The ERG is concerned that the Boolean logic is incorrect and that results have been limited to "clinical trial" in the title/abstract only. The number of records retrieved appears to be low compared to the results retrieved in other databases. **Company response:** An updated search on clinical efficacy for full text publications was conducted in Embase. As per ERG feedback, the term "hepacvirus" was added to the search, but it did not seem to yield any new records (discussed later). All records were manually screened to check for any studies which might have been missed. The search was limited to the key interventions that are currently relevant for HCV in the UK. 553 records were found and there were no missing records. The updated search terms are shown in Appendix A1. The screening results are provided in Excel A1 attached. It is likely that all HCV clinical trials are published in high impact Pubmed indexed journals; hence they were all already included in the Pubmed search.
A2	**Priority question**: Please explain why all searches in Appendix G of the company submission do not include the following interventions specified in the decision problem: paritaprevir, ribavirin, alfa 2a peginterferon and peginterferon alpha2b. **Company response:** The search of cost-effectiveness studies presented in Appendix G aimed to serve two purposes: 1. To identify published cost-effectiveness evaluations of G/P in order to determine whether there was a need for a *de novo* economic analysis in our submission; 2. To identify published evaluations of comparator therapies such that these studies could inform the development of the *de novo* economic analysis. It was considered that the most informative cost-effectiveness analyses of comparator therapies would be those that investigated DAA therapies, given that the economic analysis required for our submission included DAA comparators in the vast majority of subgroups and given that G/P itself is a DAA. Furthermore, as DAAs are a more recent advance in treatment of this condition relative to the interventions listed in the clarification question, it was considered that published cost-effectiveness analyses of DAAs would reflect the most up-to-date approaches for modelling hepatitis C and therefore be the most informative for our own model development. It should be noted that paritaprevir was in fact included in the Pubmed search (Table 211, Row 16) and Cochrane search (Table 212, Row 17) in Appendix G. For completeness, we have conducted additional searches for paritaprevir in Embase to check for any potentially missed cost effectiveness publications. This search yielded 60 results for screening, amongst which no missed studies were identified. Of the 60 results, 1 was relevant to the UK setting but had already been captured by the SLR presented in our submission. Please see Appendix A2 and Excel A2 for details of this search and search results, respectively.
A3	**Priority question**: Please clarify the syntax used for the Embase searches Appendices G, H and I of the company submission. It appears that parentheses are missing from the search strategies resulting in unusually low results in comparison to PubMed searches. The ERG is unable to replicate the searches in their current form. Please provide a search strategy that can be replicated. **Company response:** The Embase searches for the SLRs reported in Appendices G, H and I have been re-run with revised search terms, which have been tested to confirm they can be easily replicated. Please see Appendix A3 and Excel A3 for the search terms and the details of the records returned from the searches. For Appendix G, H and I, when these hits were screened no new relevant studies were identified.
A4	**Priority question**: Please provide full search strategies and number of records retrieved for EconLit and the Tufts CE Registry searches listed as sources in Appendices G, H and I of the company submission.

	Company response: The Econlit and Tufts CE registries were searched during the original SLR; however, no additional records were identified beyond those already identified via other databases. The Econlit search has now been repeated and this search, run in August 2017, identified no relevant papers (Appendix A4): the search terms 'HCV' and 'Hepatitis C' (for 2016-2017) yielded only 12 records, none of which were deemed relevant. The Tufts CE registry search was also repeated and the search results are summarised in Appendix A4. Again, no additional relevant papers were identified.
A5	Please provide URLs, full search strategies and number of records retrieved for the conference proceedings reported in Appendices D, G, H and I. The ERG notes that 549 conferences proceedings have been included in the PRISMA flow diagram for clinical SLR (Appendix D of the company submission, page 15). **Company response:** The search strategy for conference abstracts for the clinical efficacy SLR reported in Appendix D of our submission is provided in Appendix A5. The EASL 2017 abstracts were searched manually through the conference website (see below for URL). For the other 3 SLRs reported in Appendices G, H and I, the Embase search described in the submission included both full text publications and conference abstracts. EASL 2017 abstracts were searched using https://ilc-congress.eu/wp-content/uploads/2017/04/ebooks/abstract_book/22saturday/2017EASL_Saturday.pdf A total of 407 abstracts from EASL 2017 were screened
A6	Please explain why the term "hepacvirus" was not included as a MeSH term in the PubMed or Cochrane Library searches or as a free text term in PubMed, Embase or Cochrane Library searches. **Company response:** In response to this question a search has been run to investigate the impact of inclusion of the term 'hepacvirus'. This found that inclusion of this term did not yield any additional studies beyond those captured in our original SLR (please see Appendix A6).
A7	Please provide full details of the results of the Cochrane Library searches (i.e. result numbers from the individual databases). **Company response:** The searches for the Cochrane library are presented in Appendix A7; this information was presented in the appendices of our original submission. Unfortunately, at the time the Cochrane searches were run the number of results from the individual databases was not recorded. All results from the Cochrane searches were ultimately screened, regardless of which individual database they were from; we have therefore prioritised our response to other questions as this request should not materially affect the list of included and excluded studies from the SLR.
A8	Please justify the use of a trials filter in the Cochrane Library searches for clinical evidence (Appendix D, page 12-13) given that the Cochrane Library is a study design specific resource. **Company response:** The trial design key words were added because of suggestion in NICE guidance documentation that built-in filters might be appropriate where there is a need to limit to certain study designs (see section 5.2.2.7 of https://www.nice.org.uk/guidance/pmg6/resources/the-guidelines-manual-pdf-2007970804933). We had assumed that the ERG would prefer not to rely on database built-in filters. In order to check whether our use of filters resulted in any missed studies, we re-ran the search (excluding the non-relevant comparators) and removing the trial filter search terms (see Appendix A8): 601 records were found when the trial key words were removed. Of these, 561 were trial related abstracts.

	We manually screened all 561 records to check if any key publications were missed. We identified 1 study, which was missed from the initial search. The citation for the missed study is: *Hassanein et al, Daclatasvir plus sofosbuvir plus ribavirin in HCV genotype 3 infected patients with cirrhosis child a: a Randomized Trial for 16 or 24 Weeks (NCT #02304159), Hepatology, 2016, Volume 63, 1 Supplement 1* This study recruited cirrhotic GT3 patients who were either TN or TE; patients were treated with SOF + DCV for 16 or 24 weeks. Treatment with SOF + DCV for 24 weeks is included in this submission as a comparator for GT3 TN CC and GT3 TE CC patients. In the 24-week arm of the study, SVR12 amongst the 17 patients who completed the study was 100%.The SVR12 rate used in the model for SOF + DCV in both GT3 TN CC and GT3 TE CC populations is 100%. Therefore use of the SVR rate from this study in the model would not result in any change to the model results versus our base case. In conclusion, the omission of this study in the original submission does not affect the cost-effectiveness analysis results.
A9	Please clarify why the Embase strategy for clinical evidence (Appendix D, Page 12, line 69) was limited to remove conference abstracts and papers. **Company response:** The Embase strategy in Appendix D Page 12 was limited to full text papers because conference abstracts were searched separately.
A10	Please clarify how the number of Embase records reported in the PRISMA diagram for the cost effectiveness systematic literature review (Appendix G, page 174) was retrieved. The corresponding search strategy (Appendix G page 170) shows 1125557 records as the last search results retrieved. **Company response:** The search strategy presented in Appendix G of the company submission page 170 (i.e. Table 210) is an earlier version of the search strategy and was included in error. The final search strategy for Embase is presented in Appendix A10. The total number of records in Embase was 298. Please note that for the cost effectiveness review, the search was conducted with the goal to update the results of the SLR performed for TA430.
A11	Please explain the use of a cost filter in the NHS EED database (Appendix G, page 172 of the company submission). This resource is already filtered for cost studies. **Company response:** We had assumed that the ERG preferred not to rely on database built-in filters. However, to check that our use of a cost filter did not result in any missed studies, we repeated the search without using cost related keywords (See Appendix A11). The search shows 2 records, both of which are Horizon Scanning records, which are not relevant.
A12	Please clarify if the syntax “â€” used in the PubMed searches (Appendix G, page 171, line 7 and Appendix I, page 298, line 38) is a typographical error or if this is how the strategy was run. **Company response:** Pubmed searches were not conducted with “â€”. While exporting the search queries, the browser or Pubmed seems to have converted some special characters to “â€”.
A13	Please check whether “?” has been used incorrectly in PubMed searches in CS Appendix G, page 171, line 6 and CS Appendix I, page 298, line 30. Please also check if “*” has also been used incorrectly in CS Appendix H, page 260, line 9. The NLM PubMed database does not support the use of “?” or “*” as a wildcard for character substitution. Please examine if potentially relevant references have been missed as a consequence. **Company response:** We have re-run searches in order to double-check whether any studies were missed due to the use

	of "?" or "*" as a wildcard. Searches were re-run on 20th August 2017 but any returned records from after the date of our original search were ignored. For Appendix H, the re-run search was focused on EQ-5D in the interests of time; this is consistent with the approach taken in TA430. For the Appendix G and H searches, searches were re-run in PubMed. Following screening of search results, no new records were identified for either search. For Appendix I, since there were several wildcards and truncations, we repeated the PubMed search via OVID. Overall, we found 467 hits for 2016-2017, of which none were UK related resource use studies. One UK specific cost analysis was found (*Martin, Natasha K., et al. "Prioritization of HCV treatment in the direct-acting antiviral era: an economic evaluation." Journal of hepatology 65.1 (2016): 17-25);* however, this study considered the specific population of people who inject drugs (PWID). Please see Appendix A13 for updated search results.
A14	Please explain the use of the Boolean 'NOT' in the Embase Health-related quality-of-life search (Appendix H, page 259-60, line 23). This appears to exclude all articles which contain the terms "eq-5d", "eq5d" or "euroqol". **Company response:** This was a test query to check how many did not include any mention of EQ-5D related publications. The screening was done for the full set.
A15	Please explain the final set of results for the Health-related quality-of-life Cochrane Library search in Appendix H, page 261, line 20 which appears to limit the results to EQ-5D. **Company response:** We have revisited the 58 records identified prior to application of line 20 in order to also assess non--EQ-5D publications. No additional relevant records were identified.
A16	Please explain the final set of results for the Cost and healthcare resource Cochrane Library searches (Appendix I page 300) which has been limited to "hepatitis C" or "HCV" in the abstract only. The ERG is concerned that a number of relevant references may have been missed with this limit. **Company response:** The search was re-run on the Cochrane database using the same strategy as used in the previous technology assessment by NICE: TA430 (see Appendix A16). No new records were identified, thus confirming that no relevant references have been missed.
A17	Please clarify why a UK filter was applied to Cost and healthcare resource identification, measurement and valuation searches (Appendix I). **Company response:** The search has been redone without the UK filter. Please see the response to question A16 above. That said, the cost and healthcare resource use SLR aims to identify cost and resource use inputs to inform our economic analysis for the UK setting. Costs and resource use inputs are typically considered non-generalisable across jurisdictions and indeed the NICE User Guide states that the submission should describe how relevant cost and healthcare resource use data for England (our emphasis) were identified. It also notes that the search strategy may be extended to capture data from other countries, but suggests this is only required in the event that the systematic search yields limited data for England. We therefore consider that restriction of this search with a UK filter is a reasonable approach in line with NICE methods.
A18	Please explain why the search terms "China", "Asia", "Japan", "Latin", "HIV", "guidelines", "acute", "pcr", "assay"," hepatitis b" and "IL-28" have been included in the PubMed searches for Cost and healthcare resource identification, measurement and valuation (Appendix I, page 298, line 47) but have not been included in the associated Embase and Cochrane Library searches. **Company response:** This was a test query. This search has been redone using OVID so that all wildcards and truncations can be used. Please see response to question A13

A19	All literature reviews conducted in the clinical effectiveness and cost-effectiveness section were conducted as an update of the systematic literature review (SLR) conducted in TA430. This approach is based on a full reliance on the SLR results in TA430, not only in terms of search strategy but also the review process and reviewers. Please ensure that the search strategy of the submission in TA430 is in line with the search strategy of this submission and that no relevant studies that might have been interesting for this appraisal were missed or excluded in TA430. **Company response:** It should be noted that the SLR for clinical efficacy was conducted *de novo* and not as an update to the SLR conducted for TA430. The cost effectiveness, resource use and health utilities SLRs were updates of the SLRs conducted in TA430. The SLRs conducted as updates to TA430 are appropriate as the research question is the same for both appraisals.
A20	**A**. Please provide the definition of chronically infected used in the systematic review (Table 121, p14 of the appendices) **B.** Please clarify why studies of patients with renal transplant or HCV-HIV co-infected patients were excluded from the review (Table 121 p14 of the appendices), given that they were included in the NICE final scope. **Company response:** **A.** The interpretation is that any clinical studies or records which were specifically conducted only in acute HCV patients were excluded as this population is not relevant to the decision problem. **B.** It is not considered feasible to perform subgroup analyses in these special patient populations, given the existing need to stratify all analyses by genotype, cirrhosis status and treatment history, the criteria around which previous NICE treatment recommendations are based. These existing stratifications result in 6x2x2=24 primary subgroups for the base-case. This approach to comparative analysis focused on these 24 primary subgroups is consistent with TA430 and many previous NICE appraisals of DAAs. Notably, during the decision problem meeting, AbbVie understood that the ERG discussed that such an approach would be appropriate. As no comparative analyses in these special patient populations were to be conducted, it was not necessary to include such comparator studies in the SLR. It may be noted that HIV co-infected patients and patients who had received renal transplants were included in some of the studies for G/P and that evidence of efficacy is presented, although no comparative analysis is undertaken; it may be noted that SVRs were 98–100% in these studies.
A21	Please clarify why subgroup analyses was not undertaken in patients stratified by previous treatment response (non-response, partial response, relapsed), as specified in the NICE final scope. There appears to be evidence to support clinical outcomes in this population (specifically from ENDURANCE-1, -2 and -4, and EXPEDITION-1 trials). **Company response:** Neither NICE TA guidance nor the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1) provides distinct treatment recommendations on the basis of different previous treatment response. Therefore subgroup analyses were not undertaken in patients stratified by previous treatment response in order to focus the decision problem on criteria around which NICE treatment recommendations are based. It may further be noted that the main stratifications result in 24 primary subgroups and that the suggested approach would result in 48 subgroups with a consequent reduction in the patient numbers informing each TE subgroup. It is not clear what statistical power would remain in such highly stratified results. The approach applied is in line with the G/P marketing authorisation, which does not specifically restrict use to any of the stated sub-groups. Furthermore, to be meaningful for the decision problem at hand, it would also require comparator data stratified according to these criteria for all relevant comparators which would be subject to the same limitations were it to be available. Finally, during the decision problem meeting on 6 June 2017, AbbVie understood that the ERG discussed that the approach taken would be appropriate. It is also in line with the final scope, which

	specified that these subgroups may be considered only *if evidence allows*.
A22	For EXPEDITION-2, EXPEDITION-4, MAGELLAN-I and MAGELLAN-II, consider the following: • Please clarify how these studies were identified. Section B.2.2, page 36 of the company submission states that these studies were not found in the systematic review. • Were any other relevant trials identified which were not found in the systematic review (particularly studies in specific populations)? • The company submission states that 'limited information is presented for EXPEDITION-2 and MAGELLAN-II as these trials have only recently been completed. 'Please clarify when a full publication will be available for EXPEDITION-2? • Reference 43 of the submission relating to MAGELLAN-II is missing (Reau N, Kwo P, Rhee S, et al. MAGELLAN-2: safety and efficacy of glecaprevir-pibrentasvir in liver or renal transplant adults with chronic hepatitis C genotype 1-6 infection. EASL. Amsterdam, the Netherlands, 2017.). Please supply the reference. **Company response:** • These trials were undertaken by AbbVie and identified from company records of the clinical development programme. As described in Section B.2.1 on p. 36, EXPEDITION-2, EXPEDITION-4, MAGELLAN-I and MAGELLAN-II were conducted in special populations of patients with HIV co-infection, renal impairment, failure on prior DAAs (NS5A/B inhibitor and/or an NS3/4A PI) and post-transplantation (renal or liver), respectively. The results from these trials have been published, but were not identified by the SLR as trials in special populations were excluded under the SLR eligibility criteria. Furthermore, some of these publications were only published after the systematic literature review searches were completed. AbbVie considered that it was relevant to include limited information about these trials in the submission to provide supportive data for consistent efficacy of G/P across a broad patient population. • Two additional trials were described in the submission that were not found in the systematic review: CERTAIN-1 and CERTAIN-2. As described in the submission, these two trials were conducted entirely in Japanese patients, which precludes their generalisability to the UK patient population. These studies were not identified by the systematic literature review because results for these studies were first presented at a congress after the systematic literature review searches were completed. Again, AbbVie considered that it was relevant to include limited information about these trials in the submission to provide supportive data for consistent efficacy of G/P across a broad patient population. [redacted] • Reference 43 of the submission is provided in a separate file; see PDF file ''*A22_ Ref 43 of submission_Reau MAGELLAN-II*'
A23	Please provide bibliographical details of the 66 studies excluded at full paper stage in the systematic review and the reasons for exclusion (Figure 17, Appendix, page 15). **Company response:** Bibliographical details of the 66 studies are provided in Appendix A23 along with the reasons for exclusion. Upon re-review, we have now identified one record which was excluded because the same NCT number was used for two trials: an error resulted in both the LONESTAR and ATOMIC trials reporting the same NCT number. The ATOMIC trial has been added to the review: *Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial*. It should be noted that sofosbuvir with pegylated interferon alfa-2a and ribovarin is not a relevant comparator for treatment-naïve patients with hepatitis C genotype-1 infection and therefore the ATOMIC study has no implications for the economic analysis.
A24	Please clarify the following discrepancies: • Table 65, page 158 of the company submission show the SVR12 rate to be 99% (207/209) for G/P in GT1/TN/NC; but on page 108, the SVR12 is 99.1% (217/219) from ENDURANCE-1 and 96.6% (28/29) from SURVEYOR-I. The combined SVR12 rate should therefore be 98.8% (245/248).

	• Table 66, page 161 of the company submission show the SVR12 rate to be 99.2% (124/126) for G/P in GT1/TE/NC; but on page 108, the SVR12 is 99.2% (131/132) from ENDURANCE-1 and 100% (5/5) from SURVEYOR-I. Therefore the combined figure should be: 99.3% (136/137). **Company response:** • In Table 65, the SVR12 rate of 99% (207/209) for G/P in GT1/TN/NC from the ENDURANCE-1 study is based on the cohort excluding patients with HIV co-infection and patients with SOF-experience, which was a primary endpoint of ENDURANCE-1. The SVR rate of 99.1% (217/219) given on page 108 is including these patients as this is a summary page with the overall ITT population SVRs. The rationale for excluding the HIV co-infected patients and patients with previous SOF experienced in table 65 was that this table is an overview of SVR rates achieved with different regimens in TN HCV patients without HIV and SOF was included in some of the comparator treatments. • All patients co-infected with HIV in ENDURANCE-1 achieved SVR12. Data from SURVEYOR-1 was shared as additional supportive data but not included in the analysis as this phase II trial was not part of the registrational trials.
A25	Please clarify whether patients were randomised to all three treatment groups or just to the two 12 week groups in Endurance-3. If patients were not randomised to the 8 week group please explain why the 8 week G/P arm was included in the trial and why it was not part of the randomised comparison. **Company response:** The 8 week treatment group was not randomised as this arm was not part of the original trial design but was added at a later stage per discussion with regulatory authorities after encouraging phase II treatment data became available (SURVEYOR-II part 2, SVR12 of 97% (28/29) and no virological failures in TN NC GT3.).
A26	Please provide SVR12 rates for the placebo arm of ENDURANCE-2 and the SVR12 rates for the placebo arms of other AbbVie trials, where available, given that spontaneous remissions of chronic HCV infection is possible. **Company response:** SVR rates following 12 weeks placebo in ENDURANCE-2 was not collected as all these patients entered an open label 12 week treatment period with G/P. The aim of the placebo arm was not to evaluate the efficacy of treatment but rather to analyse the safety profile as spontaneous clearance in **chronic** HCV is very low. [redacted] There are no other G/P trials with placebo arms.

A27	Please explain why results from the following studies were not included in the review: - C-SURFER - NCT02092350 - C-EDGE CO-STAR - NCT02105688 - C-SCAPE, NCT01932762 - C-EDGE CO-INFECTION, NCT02105662 - ADVANCE, NCT00627926 - ALLY-2, NCT02032888 - COMMAND-4, AI444042 - LONESTAR, NCT01726517 - NCT01975675 - NCT02168361 - PILLAR, NCT00882908 - PROMISE, NCT01281839 - QUEST-1, NCT01289782 - QUEST-2, NCT01290679 - ERADICATE, NCT01878799 - RESTORE, NCT01567735 - SYNERGY, NCT01805882 - NCT02021656 - NCT01565889 - ELECTRON-2 **Company response:** Most of these studies were in special populations not relevant to the decision problem and some of the studies were in fact included in the review. Please see Appendix A27 for details.

abbvie

Priority question: For each SVR rate presented for each comparator in tables 65 and 66 (pages 157 – 160), please explain whether any other data were available, and if so, why this rate was selected. If rates from multiple studies were pooled, please explain how they were pooled and provide the calculations with data from each study separately.

Company response:
For the economic model, SVR data were drawn using the following data extraction process:

- Data from phase III data are extracted for a given patient segment, where available. [A patient segment is defined by its genotype/treatment history/cirrhosis status.]
- If more than one phase III trial exists, data are combined.
  - For instance, assuming 2 phase III trials, Trial 1: SVR=n1/N1; Trial 2: SVR=n2/N2. Then Overall SVR= (n1+n2)/(N1+N2)
- If there are no phase III data to support the label, then phase II data are extracted. We do not extract phase II data if there are phase III data in that patient segment.
- We do not extract data from other studies.
- In Tables 65 and 66, where one trial is referenced, data comes exclusively from that trial, based on the data extraction process described above.
- Where more than one trial is referenced, we provide the individual trial SVR (n/N) values.
  - In pink highlight, we show how data are (i) consolidated in cases where data come from more than one source; or (ii) computed if imputations were made

A28 **Table 65 (Company Submission): SVR inputs for TN patients using clinical trial data**

Patient population (TN)	Regimen	F0–F3 (NC)			F4 (CC)		
		Treatment duration (weeks)	SVR12 % (n/N)	Reference	Treatment duration (weeks)	SVR12 % (n/N)	Reference
GT1	G/P	8	[redacted]	ENDURANCE-1 ITT-PS TN population[46]	12	[redacted]	EXPEDITION-1 ITT TN population[57]
	OBV/PTV/RTV + DSV ± RBV	1a: 12 (+ RBV) 1b: 12	[redacted] GT1a = 405/422 GT1b = 209/209 %GT1a =68.1%	GT1a: Pooled data from PEARL-IV (CSR)[130] and SAPPHIRE-I (CSR)[135] GT1b: PEARL-III (CSR)[129]	1a: 24 (+ RBV) 1b: 12	96.4%[a] GT1a = 53/56 GT1b = 27/27 %GT1a =68.1%	GT1a and G1b: TURQUOISE-II[131]
	EBR/GZR	12[b]	93.2%[c]	C-EDGE TN (US	12[b]	95.9%[c]	C-EDGE TN (US

				GT1a SVR = 91.0% GT1b SVR = 98.0% %GT1a = 68.1% GT1a NC imputation: GT1a NC+CC SVR = 144/157=91.7% GT1 NC SVR = 207/220=94.1% GT1 CC SVR = 66/68=97.1% Assume %GT1a NC (vs CC) same as % GT1 NC = 220/288 (=76.4%) GT1a NC SVR = 144/157-((1-220/288)*(66/68-207/220)) = 91.0% GT1b NC imputation: GT1b NC+CC = 129/131 GT1b CC = 100% (=30.9/30.9) – see corresponding GT1b CC imputation. GT1b NC SVR = (129-30.9)/(131-30.9)=98.1/100.1 =98.0%	PI)[139]		GT1a SVR = 94.0% GT1b SVR =100 .0% %GT1a = 68.1% GT1a CC imputation: GT1a NC+CC SVR = 144/157=91.7% GT1 NC SVR = 207/220=94.1% GT1 CC SVR = 66/68=97.1% Assume %GT1a NC (vs CC) same as % GT1 NC = 220/288 (=76.4%) GT1a NC SVR = 144/157-((220/288)*(207/220-66/68)) = 94.0% GT1b CC imputation: GT1b NC+CC SVR = 129/131=98.5% GT1 NC SVR = 207/220=94.1% GT1 CC SVR = 66/68=97.1% Assume %GT1b NC (vs CC) same as % GT1 NC = 220/288 (=76.4%) GT1a NC SVR = 129/131-((220/288)*(207/220-66/68)) = 100.7%. Since SVR<=100%, we assume GT1NC SVR=100%	PI)[139]	
	SOF/LDV	8	F0–F1: 95.2% (80/84) F2–F3: 94.4% (68/72)	ION-3[142]	12	94.1% (32/34)	ION-1[140]	
	SOF/VEL	12	98.4% (251/255)[d]	ASTRAL-1[144]	12	98.6% (72/73)[d]	ASTRAL-1[144]	

GT2	**G/P**	8	[redacted] SURVEYOR-II: Arm J SVR = 46/47; Arm S SVR = 126/127 Overall SVR = (46+126)/(47+127)=172/174	SURVEYOR-II, pooled data from ITT TN population in Parts 2 and 4[64]	12	[redacted]	EXPEDITION-1 ITT TN population[57]
	SOF/VEL	12	99.0% (99/100)[d]	ASTRAL-2[145]	12	100.0% (15/15)[d]	ASTRAL-2[145]
	SOF + RBV	12	96.3% (180/187) FISSION: SVR = 59/61 VALENCE: SVR = 29/30 ASTRAL-2: SVR = 92/96 Overall SVR: (59+29+92)/(61+30+96)=180/187	Pooled data from FISSION (Sovaldi SmPC),[150] VALENCE[149] and ASTRAL-2 (TA430)[1]	12	89.7% (26/29) FISSION: SVR = 10/12 VALENCE: SVR = 2/2 ASTRAL-2: SVR = 14/15 Overall SVR: (10+2+14)/(12+2+15)=26/29	Pooled data from FISSION (Sovaldi SmPC),[150] VALENCE[149] and ASTRAL-2 (TA430)[1]
	Peg-IFN + RBV	24	81.5% (44/54)	FISSION (Sovaldi SmPC)[150]	Not a comparator		
GT3	**G/P**	8	94.9% (149/157)	ENDURANCE-3 ITT population[52, 88]	12	[redacted] SURVEYOR-II: Arm D SVR = 24/24; Arm Q1 SVR = 39/40 Overall SVR = (24+39)/(24+40)=63/64	SURVEYOR-II, pooled data from ITT TN population in Parts 2 and 3[64]
	SOF/VEL	12	98.2% (160/163)	ASTRAL-3[145]	12	96.7% (116/120) ASTRAL-3 SVR = 40/43 POLARIS-3 SVR =76/77 Overall SVR= (40+76)/(43+77) =116/120	Pooled data from ASTRAL-3[145] and POLARIS-3[146, 147]
	SOF + DCV ± RBV	12	96.8% (184/190) ENDURANCE-3, SVR = 111/115; ALLY-3, SVR=73/75 Overall SVR= (111+73)/(115+75)=184/190	Pooled data from ENDURANCE-3 ITT population[52, 88] and ALLY-3[155]	24 (+ RBV)	100% (5/5)	A1444040[156]
	SOF + RBV	Not a comparator			24	77.6% (45/58)	Pooled data from

						VALENCE SVR =12/13 ASTRAL-3 SVR =33/45 Overall SVR = (12+33)/(13+45)=45/58	VALENCE (Sovaldi SmPC)[150] and ASTRAL-3 (TA430)[1]
	SOF + peg-IFN + RBV	Not a comparator			12	91.3% (21/23)	BOSON[148]
GT4	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TN population[64]	12	[redacted]	EXPEDITION-1 ITT TN population[57]
	OBV/PTV/RTV + RBV	12	100.0% (42/42)[a, e]	PEARL-I[124]	12	96.7% (29/30)[a]	AGATE-I[28]
	EBR/GZR	12[b]	100.0% (16.71/16.71)[f] GT4 F0-F4 SVR=18/18. Proportion of F0-F3 GT4/6 in C-EDGE TN = 92.9% (26/28). Thus 18*(26/28)=16.71	C-EDGE TN (Zeuzem et al. [215] and US PI)[84, 139]	12[b]	100.0% (1.29/1.29)[f] GT4 F0-F4 SVR=18/18. Proportion of F4 GT4/6 in C-EDGE TN = 7.1% (2/28) Thus 18*(2/28) =1.29	C-EDGE TN (Zeuzem et al. [215] and US PI)[84, 139]
	SOF/LDV	Not a comparator			12	100.0% (1/1)	Study 1119[158]
	SOF/VEL	12	100.0% (89/89)[d]	ASTRAL-1[144]	12	100.0% (27/27)[d]	ASTRAL-1[144]
GT5	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TN population[64]	12	[redacted]	EXPEDITION- ITT TN population[57]
	SOF/VEL	12	96.6% (28/29)[d]	ASTRAL-1[144]	12	100.0% (5/5)[d]	ASTRAL-1[144]
	SOF + peg-IFN + RBV	Not a comparator			12	50% (1/2)[g]	NEUTRINO (Sovaldi SmPC)[150]
GT6	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TN population[64]	12	[redacted]	EXPEDITION-1 ITT TN population[57]
	SOF/VEL	12	100.0% (35/35)[d]	ASTRAL-1[144]	12	100.0% (6/6)[d]	ASTRAL-1[144]
	SOF + peg-IFN + RBV	Not a comparator			12	50% (1/2)[g]	NEUTRINO (Sovaldi SmPC)[150]

[a]SVR in GT1 patients is calculated using a weighted average of SVRs in GT1a and GT1b patients, and n/N is not reported; [b]For simplicity, the model assumes all patients receive EBR/GZR for 12 weeks; [c]SVR in GT1 patients is calculated using a weighted average of SVRs in GT1a and GT1b patients, and n/N is not reported; [d]Data available included the following: (i) SVR data stratified by cirrhosis status for TN and TE patients combined and (ii) overall SVR data stratified by TN and TE patients. The former were used and it was assumed that TN=TE; [e]'RBV-eligible' patients; [f]The number of GT4 NC and CC patients was calculated, assuming the percentage of CC patients was the same between GT4 and GT6 patients. The percentage of CC patients among GT4 and GT6 patients was calculated from the percentage of patients among the GT1, GT4 and GT6 patient population available in the trial publication[84] and the percentage of patients among the GT1 population available in the US package insert.[139] The calculated n/N is reported to 2 decimal places; [g]Data for overall GT4, GT5 and GT6 population.

Abbreviations: CC, compensated cirrhosis; CSR, clinical study report; DAA, direct-acting antiviral; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ITT, intention-to-treat; ITT-PS, ITT mono-infected GT1 DAA-naïve; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PI package insert; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SmPC, summary of product characteristics; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

Table 66 (Company Submission): SVR inputs for TE patients using clinical trial data

Patient population (TE)	Regimen	F0–F3 (NC)			F4 (CC)		
		Treatment duration (weeks)	SVR12 % (n/N)	Reference	Treatment duration (weeks)	SVR12 % (n/N)	Reference
GT1	G/P	8	[redacted]	ENDURANCE-1 ITT-PS TE population[46]	12	[redacted]	EXPEDITION-1 ITT TE population[57]
	OBV/PTV/RTV + DSV ± RBV	1a: 12 (+ RBV) 1b: 12	97.4%[a,b] GT1 TE SVR: Weighted average of GT1_Null, GT1_Partial, GT1_Prior %Null =30% %Partial = 30% %Prior = 40% GT1_Null: weighted average of: GT1a = 83/87 GT1b = 32/32 %GT1a =68.1% GT1_Partial: weighted average of:	GT1a: SAPPHIRE-II[136] GT1b: PEARL-II[126]	1a: 24 (+ RBV) 1b: 12	98.5%[a,b] GT1 TE SVR: Weighted average of GT1_Null, GT1_Partial, GT1_Prior %Null =30% %Partial = 30% %Prior = 40% GT1_Null: weighted average of: GT1a = 39/42 GT1b = 10/10 %GT1a =68.1% GT1_Partial:	GT1a: TURQUOISE-II[131] GT1b: TURQUOISE-III[27]

					GT1a = 36/36 GT1b = 26/26 %GT1a =68.1% GT1 Prior: weighted average of GT1a = 47/50 GT1b = 33/33 %GT1a =68.1%			weighted average of: GT1a = 10/10 GT1b = 8/8 %GT1a =68.1% GT1 Prior: weighted average of GT1a = 13/13 GT1b = 5/5 %GT1a =68.1%	
		EBR/GZR	12[c]	93.4%[d] GT1a SVR = 90.3% GT1b SVR = 100% %GT1a = 68.1% GT1a NC imputation: GT1a NC+CC SVR = 55/61=90.2% GT1 NC SVR = 61/65=93.8% GT1 CC SVR = 29/31=93.5% Assume %GT1a NC (vs CC) same as % GT1 NC = 65/96 (=67.7%) GT1a NC SVR = 55/61-((1-65/96)*(29/31-61/65)) = 90.3% GT1b NC imputation: GT1b NC+CC SVR = 34/34 % NC (vs CC) = 65/96 = 67.7% GT1b n=N=(1-65/96)*34 = 11.0	C-EDGE TE (US PI)[139]	12[c]	93.2%[d] GT1a SVR = 90.0% GT1b SVR = 100% %GT1a = 68.1% GT1a CC imputation: GT1a NC+CC SVR = 55/61=90.2% GT1 NC SVR = 61/65=93.8% GT1 CC SVR = 29/31=93.5% Assume %GT1a NC (vs CC) same as % GT1 NC = 65/96 (=67.7%) GT1a NC SVR = 55/61-((65/96)*(61/65-29/31)) = 90.0% GT1b CC imputation: GT1b NC+CC SVR = 34/34 % NC (vs CC) = 65/96 = 67.7% GT1b n=N=(65/96)*34 =	C-EDGE TE (US PI)[139]

							23.0	
		SOF/LDV	12	95.4% (83/87)	ION-2[141]	12	86.4% (19/22)	ION-2[141]
		SOF/VEL	12	98.4% (251/255)[e]	ASTRAL-1[144]	12	98.6% (72/73)[e]	ASTRAL-1[144]
	GT2	**G/P**	8	[redacted] SURVEYOR-II: Arm J SVR = 7/7; Arm S SVR = 14/16 Overall SVR = (7+14)/(7+16) =21/23	SURVEYOR-II, pooled data from ITT TE population in Part 2 and Part 4[64]	12	[redacted]	EXPEDITION-1 ITT TE population[57]
		SOF/VEL	12	100.0% (15/15)[e]	ASTRAL-2[145]	12	100.0% (4/4)[e]	ASTRAL-2[145]
		SOF + RBV	12	88.5% (69/78) FUSION: SVR = 26/29 VALENCE: SVR = 30/33 ASTRAL-2: SVR = 13/16 Overall SVR: (26+30+13)/(29+31+16) =69/78	Pooled data from FUSION (Sovaldi SmPC),[150] VALENCE (Sovaldi SmPC)[150] and ASTRAL-2 (TA43)[1]	12	77.3% FUSION: SVR = 6/10 VALENCE: SVR = 7/8 ASTRAL-2: SVR = 4/4 Overall SVR: (6+7+4)/(10+8+4) =17/22=77.3%	Pooled data from FUSION (Sovaldi SmPC),[150] VALENCE (Sovaldi SmPC)[150] and ASTRAL-2 (TA43)[1]
	GT3	**G/P**	16	95.5% (21/22)	SURVEYOR-II, Part 3 ITT TE population[64, 65]	16	[redacted] SURVEYOR-II: Arm O SVR = 3/4; Arm R2 SVR = 45/47 Overall SVR = (3+45)/(4+47) =48/51	SURVEYOR-II, pooled data from ITT TE population in Parts 2 and 3[64]
		SOF/VEL	12	91.2% (31/34)	ASTRAL-3[145]	12	89.9% (62/69) ASTRAL-3 SVR = 33/37 POLARIS-3 SVR =29/32 Overall SVR= (33+29)/(37+32) =62/69	Pooled data from ASTRAL-3[145] and POLARIS-3[146, 147]

		SOF + DCV ± RBV	12	94.1% (32/34)	ALLY-3[155]	24 (+ RBV)	100% (5/5)[f]	A1444040[156]
		SOF + RBV	Not a comparator			24	59.0% (49/83) VALENCE SVR =27/45 ASTRAL-3 SVR =22/38 Overall SVR = (27+22)/(45+38) =49/83	Pooled data from VALENCE (Sovaldi SmPC)[150] and ASTRAL-3 (TA430)[1]
		SOF + peg-IFN + RBV	Not a comparator			12	85.7% (30/35)	BOSON[148]
	GT4	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TE population[64]	12	[redacted]	EXPEDITION-1 ITT TE population[57]
		OBV/PTV/RTV + RBV	12	100.0% (49/49)[a, b]	PEARL-I[124]	12	98.2% (N=29)[a, b, h] GT4 TE SVR: Weighted average of GT4_Null, GT4_Partial, GT4_Prior %Null =30% %Partial = 30% %Prior = 40% GT4_Null = 16/17 GT4_Partial: 5/5 GT4_Prior: 7/7	AGATE-I[28]
		EBR/GZR	12[c]	100.0% (3.00/3.00)[i] Assume % GT4 NC (vs CC) same as % GT4/6 NC, i.e 33.3% (=3/9) Number of GT4 NC+CC= 9. Thus, number of GT4 NC =9* (3/9) =3 GT4 NC SVR = 100% (= 3/3)	C-EDGE TE (Kwo et al. [2016] and US PI)[138, 139]	12[c]	66.7% (4.00/6.00)[i] GT4 NC+CC SVR=7/9. GT4 NC SVR=3/3 Thus GT4 CC=4/6	C-EDGE TE[138, 139]
		SOF/LDV	12	84.6% (11/13)	Study 1119[158]	12	100.0% (9/9)	Study 1119[158]

	SOF/VEL	12	100.0% (89/89)[e]	ASTRAL-1[144]	12	100.0% (27/27)[e]	ASTRAL-1[144]
GT5	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TE population[64]	12	[redacted]	EXPEDITION-1 ITT TE population[57]
	SOF/VEL	12	100.0% (11/11)[e]	ASTRAL-1[144]	12	100.0% (11/11)[e]	ASTRAL-1[144]
	SOF + peg-IFN + RBV	Not a comparator			12	50% (1/2)[j]	NEUTRINO (Sovaldi SmPC)[150]
GT6	**G/P**	8	[redacted]	SURVEYOR-II, Part 4 ITT TE population[64]	12	[redacted]	EXPEDITION-1 ITT TE population[57]
	SOF/VEL	12	100.0% (35/35)[e]	ASTRAL-1[144]	12	100.0% (6/6)[e]	ASTRAL-1[144]
	SOF + peg-IFN + RBV	Not a comparator			12	50% (1/2)[j]	NEUTRINO (Sovaldi SmPC)[150]

[a]SVR in GT1 patients is calculated using a weighted average of SVRs in GT1a and GT1b patients, and n/N is not reported; [b]Data are weighted among null response, partial response and prior relapse patients; [c]For simplicity, the model assumes all patients receive EBR/GZR for 12 weeks; [d]SVR in GT1 patients is calculated using a weighted average of SVRs in GT1a and GT1b patients, and n/N is not reported; [e]Data available included the following: (i) SVR data stratified by cirrhosis status for TN and TE patients combined and (ii) overall SVR data stratified by TN and TE patients. The former were used and it was assumed that TN=TE, except in GT5 TE where the latter is used. This is done because the SVR rate in this subgroup is 100% and using the data in (i) would imply an SVR rate below 100% (whereas one F0–F3 TN patient did not achieve SVR); [f]Assumed to be the same as for TN; [g]There were low numbers of GT4, GT5 and GT6 TE patients recruited, so pooled results from GT4-, GT5- and GT6-infected patients were used; [h]In GT4 F4 where SVR≠100%, only the consolidated 'N' is reported; [i]The number of GT4 NC and CC patients was calculated, assuming the percentage of CC patients was the same between GT4 and GT6 patients. The percentage of CC patients among GT4 and GT6 patients was calculated from the percentage of patients among the GT1, GT4 and GT6 patient population available in the trial publication[138] and the percentage of patients among the GT1 population available in the US package insert;[139] [j]Assumed to be the same as TN (data for overall GT4, GT5 and GT6 population), same assumption as TA430[1]

Abbreviations: CC, compensated cirrhosis; CSR, clinical study report; DCV, daclatasvir; DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; ITT, intention-to-treat; ITT-PS, ITT mono-infected GT1 DAA-naïve; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

abbvie

A29

Priority question: For each adverse event presented for each comparator in tables 67 and 68 (pages 163 – 164), please explain whether any other data were available, and if so, why this rate was selected. If rates from multiple studies were pooled, please explain how they were pooled and provide the calculations with data from each study separately.

Company response:
The same data extraction methodology (see response to A28) was applied to adverse event (AE) data insofar as phase III data are extracted. Phase II data are extracted only in the absence of phase III data. We do not extract data from other types of studies.

Trials report AE by trial arm: in the absence of data, we assume that AE rates in each patient segment within a trial arm are equal, which imply AE rates are independent of genotype/treatment history/cirrhosis status. E.g., In C-EDGE TN, AE data for GT1 and GT4 combined; in ASTRAL-1, AE data for GT1,4,5,6 in TN/TE and NC/CC are combined

For G/P, we extracted data from the CSR.

Text in Pink highlights patient segments where AE data are pooled from more than one trial or if imputation was made to derive final data input.

Table 68 (Company Submission): Inputs for AEs in TN patients using clinical trial data

Patient pop (TN)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropoenia	Grade 3/4 thrombocy-topaenia	Reference
GT1	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ENDURANCE-1[46]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	OBV/PTV/RTV + DSV ± RBV	NC	3.84% GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: SAPPHIRE-1: 25/473 PEARL-IV: 6/100 Overall: 31/573 GT1b:	7.88% GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: SAPPHIRE-1: 51/473 PEARL-IV: 5/100 Overall: 56/573 GT1b: PEARL-III: 8/209	0.00%	0.15% GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: SAPPHIRE-1: 0/473 PEARL-IV: 0/100 Overall: 0/573 GT1b: PEARL-III: 1/209	0.15% GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: SAPPHIRE-1: 0/473 PEARL-IV: 0/100 Overall: 0/573 GT1b: PEARL-III: 1/209	Pooled data from SAPPHIRE-I[134] and PEARL-IV[128]; weighted average with PEARL-III[128]

				PEARL-III: 1/209					
			CC	7.13% GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: TURQ-II:18/172 GT1b: TURQ-III: 0/60	10.96% GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: TURQ-II:25/172 GT1b: TURQ-III: 2/60	4.75% GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: TURQ-II:12/172 GT1b: TURQ-III: 0/60	1.19% GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: TURQ-II:3/172 GT1b: TURQ-III: 0/60	1.06% GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: TURQ-II:0/172 GT1b: TURQ-III: 2/60	TURQUOISE-II[131]
		EBR/GZR	**NC**	2.85%	0.00%	0.00%	0.32%	0.00%	C-EDGE TN[84]
			CC	2.85%	0.00%	0.00%	0.32%	0.00%	
		SOF/LDV	**NC**	0.93%	1.40%	0.00%	0.00%	0.00%	ION-3[142]
			CC	0.47%	4.88%	0.00%	0.47%	0.23%	ION-1[140]
		SOF/VEL	**NC**	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
			CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	GT2	**G/P**	**NC**	[redacted] Arm J: 0/54 Arm S:1/203 Overall: 1/257	[redacted] Arm J: 0/54 Arm S:1/203 Overall: 1/257	[redacted] Arm J: 0/54 Arm S:5/203 Overall: 5/257	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 4[64]
			CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
		SOF/VEL	**NC**	0.00%	0.00%	0.00%	0.00%	0.00%	ASTRAL-2[145]
			CC	0.00%	0.00%	0.00%	0.00%	0.00%	
		SOF + RBV	**NC**	4.24% FISSION: 20/256 VALENCE: 0/84 ASTRAL-2: 0/132 Overall = 20/472	4.87% FISSION: 23/256 VALENCE: 0/84 ASTRAL-2: 0/132 Overall = 23/472	3.18% FISSION: 14/256 VALENCE: 0/84 ASTRAL-2: 1/132 Overall = 15/472	0.21% FISSION: 0/256 VALENCE: 1/84 ASTRAL-2: 0/132 Overall = 15/472	0.00%	Pooled data from FISSION,[151] VALENCE[149] and ASTRAL-2[151]
			CC	4.24% See above: NC TN	4.87% See above: NC TN	3.18% See above: NC TN	0.21% See above: NC TN	0.00% See above: NC TN	
		Peg-IFN +	**NC**	11.52%	17.70%	13.99%	14.81%	7.41%	FISSION[154]

		RBV							
	GT3	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ENDURANCE-3 [52, 88]
			CC	[redacted]	[redacted] Arm O: 2/24 Arm Q: 1/62 Overall: 3/86	[redacted]	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 3[64]
		SOF/VEL	NC	0.00%	0.00%	0.00%	0.26% ASTRAL-3 = 0/277 POLARIS-3 = 1/109 Overall = 1/(277+109)=0.26%	0.52% ASTRAL-3 = 1/ POLARIS-3 = 1/ Overall =2/386=0.52%	Pooled data from ASTRAL-3[145] and POLARIS-3[146, 147]
			CC	0.00%	0.00%	0.00%	0.26% See above: NC TN	0.52% See above: NC TN	
		SOF + DCV ± RBV	NC	0.00%	0.75% END-3: 2/115 ALLY-3: 0/152 Overall: 2/267	0.00%	0.00%	0.75% END-3: 0/115 ALLY-3: 2/152 Overall: 2/267	Pooled data from ENDURANCE-3 [52, 88] and ALLY-3[155]
			CC	7.14%	0.00%	14.29%	0.00%	0.00%	A1444040[156]
		SOF + RBV	CC	0.00%	0.00%	0.19% VALENCE: 0/250 ASTRAL-3: 1/275 Overall = 1/525	0.00%	0.76% VALENCE: 3/250 ASTRAL-3: 1/275 Overall = 4/525	Pooled data from VALENCE[149]and ASTRAL-3[145]
		SOF + peg-IFN + RBV	CC	0.00%	19.80%	0.51%	15.74%	4.57%	BOSON[148]
	GT4	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
			CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
		OBV/PTV/RTV + RBV	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	PEARL-I (CSR)[125]
			CC[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AGATE-I (CSR)[123]
		EBR/GZR	NC	2.85%	0.00%	0.00%	0.32%	0.00%	C-EDGE TN[84]
			CC	2.85%	0.00%	0.00%	0.32%	0.00%	
		SOF/LDV	CC	0.00%	0.00%	0.00%	0.00%	4.55%	Study 1119[158]
		SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
			CC	0.00%	0.00%	0.00%	0.64%	0.16%	

GT5	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	CC	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[153]
GT6	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	CC	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[153]

Note: For published references, if AEs were not reported (for example because only AEs affecting >5% of patients were reported), these were assumed to have a frequency of 0.

Abbreviations: AEs, adverse events; CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TN, treatment-naïve; VEL, velpatasvir

Table 69 (Company Submission): Inputs for AEs in TE patients using clinical trial data

Patient pop (TE)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropoenia	Grade 3/4 thrombocy-topaenia	Reference
GT1	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ENDURANCE-1[46]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	OBV/PTV/RTV + DSV ± RBV	NC	3.67% GT1 AE: Weighted average of GT1a and	6.30% GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1%	0.00%	0.00%	0.00%	Weighted average of PEARL-II[126] and SAPPHIRE-II[136]

				GT1b, where % GT1a=68.1% GT1a: SAPPHIRE-II: 16/297 GT1b: PEARL-II: 0/95	GT1a: SAPPHIRE-II: 26/297 GT1b: PEARL-II: 1/95				
			CC	[redacted] GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: TURQ-II:18/172 GT1b: TURQ-III: 0/60	[redacted] GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: TURQ-II:25/172 GT1b: TURQ-III: 2/60	[redacted] GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: TURQ-II:12/172 GT1b: TURQ-III: 0/60	[redacted] GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: TURQ-II:3/172 GT1b: TURQ-III: 0/60	[redacted] GT1 AE: Weighted average of GT1a and GT1b, where % GT1a=68.1% GT1a: TURQ-II:0/172 GT1b: TURQ-III: 2/60	TURQUOISE-III (Feld et al. [2016][27] and CSR[133])
		EBR/GZR	**NC**	0.00%	0.00%	0.00%	0.00%	0.00%	C-EDGE TE[138]
			CC	0.00%	0.00%	0.00%	0.00%	0.00%	
		SOF/LDV	**NC**	0.00%	1.83%	0.00%	0.00%	0.92%	ION-2[141]
			CC	0.00%	1.83%	0.00%	0.00%	0.92%	
		SOF/VEL	**NC**	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
			CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	GT2	**G/P**	**NC**	[redacted] See GT2 NC TN	[redacted] See GT2 NC TN	[redacted] See GT2 NC TN	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 4[64]
			CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
		SOF/VEL	**NC**	0.00%	0.00%	0.00%	0.00%	0.00%	ASTRAL-2[145]
			CC	0.00%	0.00%	0.00%	0.00%	0.00%	
		SOF + RBV	**NC**	3.45%	2.19%	2.19%	0.63%	0.63%	Pooled data from

			CC	3.45%	2.19%	2.19%	0.63%	0.63%	FUSION,[151] VALENCE[149] and ASTRAL-2[151]
	GT3	**G/P**	**NC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 3[64]
			CC	[redacted] FUSION: 11/103 VALENCE: 0/84 ASTRAL-2: 0/132 Overall = 11/319	[redacted] Arm 0: 0/4 Arm R: 1/69 Overall: 1/73	[redacted] Arm 0: 0/4 Arm R: 1/69 Overall: 1/73	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 3[64]
		SOF/VEL	**NC**	0.00%	0.00%	0.00%	0.26% See GT3 NC TN	0.52% See GT3 NC TN	Pooled data from ASTRAL-3[145] and POLARIS-3[146, 147]
			CC	0.00%	0.00%	0.00%	0.26% See GT3 NC TN	0.52% See GT3 NC TN	
		SOF + DCV ± RBV	**NC**	0.00%	0.00%	0.00%	0.00%	1.32%	ALLY-3[155]
			CC	7.14%	0.00%	14.29%	0.00%	0.00%	A1444040[156]
		SOF + RBV	**CC**	0.00%	0.00%	0.19% See GT3 CC TN	0.00%	0.76% See GT3 CC TN	Pooled data from VALENCE[149]and ASTRAL-3[145]
		SOF + peg-IFN + RBV	**CC**	0.00%	19.80%	0.51%	15.74%	4.57%	BOSON[148]
	GT4	**G/P**	**NC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
			CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
		OBV/PTV/RTV + RBV	**NC[c]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	PEARL-I(CSR)[125]
			CC[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AGATE-I (CSR)[123]
		EBR/GZR	**NC**	0.00%	0.00%	0.00%	0.00%	0.00%	C-EDGE TE[138]
			CC	0.00%	0.00%	0.00%	0.00%	0.00%	
		SOF/LDV	**NC**	0.00%	0.00%	0.00%	0.00%	4.55%	Study 1119[158]
			CC	0.00%	0.00%	0.00%	0.00%	4.55%	

	SOF/VEL	**NC**	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
GT5	**G/P**	**NC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	SOF/VEL	**NC**	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	**CC**	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[153]
GT6	**G/P**	**NC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[64]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[57]
	SOF/VEL	**NC**	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[144]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	**CC**	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[153]

Note: For published references, if AEs were not reported (for example because only AEs affecting >5% of patients were reported), these were assumed to have a frequency of 0.

Abbreviations: AEs, adverse events; CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; VEL, velpatasvir

A30	In Table 59 (page 148 -149), genotype 2 is split for 'Comparators for IFN-eligible patients' and 'Comparators for IFN-ineligible patients'; but Tables 65 and 66 (pages 158 – 163) do not report separate results for these two groups. Please clarify whether the same result for SOF/VEL was used **Company response:** In the economic model, there is no distinction between IFN-eligible and IFN-ineligible patients. Thus, Tables 65 and 66 reported them together.
A31	**A.** Please clarify how SVR12 is estimated to be 77.3% for SOF+RBV in GT2/TE/CC in Table 66 (page 161 of the company submission). The reference states: "Pooled data from FUSION (Sovaldi SmPC),150 VALENCE (Sovaldi SmPC)150 and ASTRAL-2 (TA43)1". However, according to Table 130 (Appendix D.1.1.4, page 60) SVR12 rates for these three studies are 100%, 93% and 94%, respectively. If the raw data from the individual studies are reported in the company submission, please explain where; if not, please provide them in all instances where data are pooled. **B.** Please clarify how SVR12 is estimated to be 96.8% (184/190) for SOF + DCV in Table 65 (, page 159 of the company submission). According to the reference it is "Pooled data from ENDURANCE-3 ITT population52, 88 and ALLY-3155". However, according to Table 130 (Appendix D.1.1.4, page 60) SVR12 rates for SOF + DCV are 99% (N=101) for ALLY-3 (i.e. 100/101) and according to Table 31 (CS, page 112) 96.5% (111/115) for ENDURANCE-3. The pooled result would then be: 211/216 = 97.7%. **Company response:** A. SVR for GT2/TE/CC in the economic model: ▪ FUSION: SVR = 6/10 ▪ VALENCE: SVR = 7/8 ▪ ASTRAL-2: SVR = 4/4 ▪ Overall SVR: (6+7+4)/(10+8+4)=17/22=77.3% See also response to A28 B. GT3 TN NC SOF+DCV**:** ▪ ENDURANCE-3, SVR = 111/115. Data aligns with table 31 (CS page 112) ▪ ALLY-3, SVR=73/75. Data for ALLY-3 in Appendix D.1.1.4, where N=101, combines NC (N=75) and CC (N=19) patients. We only use data for NC patients ▪ Overall SVR= (111+73)/(115+75)=184/190
A32	**Priority question**: The company states that naïve indirect comparisons were used to compare effectiveness of interventions. However, no results of these naïve indirect comparisons are reported. Please provide the results for each comparison in each population. And please complete section B.2.10.1 (Uncertainties in the indirect and mixed treatment comparisons). **Company response:** We believe this question is related to the following sentence from Section B.2.10: 'Ultimately, the approach taken in this submission of using naïve indirect comparisons to inform treatment effect estimates, although associated with acknowledged limitations, is consistent with the approach frequently seen in appraisals of therapies for the treatment of CHC.' To clarify, the SVR rates used in the economic model are naïve, raw SVR rates taken directly from individual trials of G/P or comparator therapies for the subgroup in question. The economic model implicitly makes a naïve comparison as alluded to in the quoted sentence, but the SVR rates themselves were not informed by an indirect comparison, which was not feasible, as described in Section B.2.10. No indirect comparison was undertaken, therefore we have not completed section B.2.10.1. AbbVie acknowledges that the selection of SVR rates from across different trials outside of a network meta-analysis framework means that results are open to the same risks of bias as would be associated with observational studies. However, the infeasibility of forming a network comparison is a common feature of previous technology appraisals for DAA therapies in CHC, and using naïve

	SVR rates directly from individual studies in economic models is an alternative that has been considered acceptable by previous NICE Committees and accepted as part of the TA430. Notably, in the recent appraisal of the pan-genotypic regimen SOF/VEL (TA430), a network was only feasible in two groups, and even though it was technically possible to form a network, this network was associated with such limitations as a result of trial heterogeneity that the NICE Committee agreed that it would be inappropriate for the outputs of the indirect treatment comparison to inform the cost-effectiveness model. Naïve, raw SVR rates taken directly from individual trials were considered preferable. Our submission is aligned with this approach given that an indirect comparison was not feasible in any subgroup.
A33	The following comparators were included in the NICE scope but excluded from the company submission on the basis that they are not used in current NHS practice (Table 1, page 20). Please reconsider whether it is appropriate to include these comparators or provide evidence to support the case for excluding them from the clinical and cost effectiveness review. • Daclatasvir in combination with sofosbuvir, with or without ribavirin (for specific people with genotype 1, or 4; as recommended by NICE) • Peginterferon alfa with ribavirin (for genotypes 1– 6). The committee in TA430 concluded that PR is a relevant comparator across all subgroups. Excluding this comparator suggests the evidence presented is for interferon ineligible patients only. • Sofosbuvir in combination with ribavirin, with or without peginterferon alfa (for specific people with genotypes 1–6; as recommended by NICE). **Company response:** Given the large number of subgroups in the submission, AbbVie considered the additional complexity that would be added to the submission if further historical comparators were included. As justified below, the historical comparators in question *are not currently used in clinical practice in England* and are therefore outwith the NICE Methods Guide which considers "established practice in the NHS". Therefore, the approach as taken in the submission – to consider only the comparators that are in fact currently used in clinical practice – has been maintained, and these historical comparators have not been included. **Daclatasvir in combination with sofosbuvir, with or without ribavirin (for specific people with genotype 1, or 4; as recommended by NICE)** This comparator was not considered relevant for GT4 because it is not used in clinical practice in England for GT4 patients. Notably, the resource impact template (RIT) published as part of TA430, with estimates based on current notification trends in 2016/2017, expected no use of this comparator in GT4 patients. This further is supported by expert clinical opinion and the absence of this treatment as a recommended option for patients with GT4 infection in the June 2017 BASL guidelines, and in the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1)., which also includes an NHS England (NHSE) determined 'rate card'. The 'rate card' is an NHSE term used to describe therapies which were awarded contracts with NHSE based on the tender outcomes. The 'rate card' also assigns a sequence of use, i.e. it specifies 1st, 2nd and 3rd line treatment and there is a CQUIN (Commissioning for Quality and Innovation payments framework) which incentivises the alignment of specialist led multidisciplinary team (MDT) decisions with NHS England published rate cards. It is therefore reasonable to assume that only therapies listed on the rate card will be used within NHSE and form current clinical practice. Notably, during the decision problem meeting, AbbVie understood that the ERG discussed that the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1) were an appropriate source for selecting comparators that are relevant to clinical practice in England. The TA430 RIT did predict use of this comparator in GT1. However, this was based on an older version of the Hepatitis C Guidelines and treatment practice in this area is rapidly evolving. The older guidelines were superseded by the **June 2017** Eastern Liver Network Hepatitis C Guidelines (v 8.1). The updated Guidelines no longer recommend this comparator as a treatment for GT1 patients; this is a more recent source than the predictions in the TA430 RIT, and supports the fact that this comparator is not used in clinical practice in England anymore. This comparator is also not a recommended treatment option for GT1 patients in the June 2017 BASL guidelines. As stated in the submission, this comparator is not relevant for GT1. **Peginterferon alfa with ribavirin (for genotypes 1–6)**

The evidence presented in the submission supports the use of G/P irrespective of IFN-eligibility; AbbVie strongly refute the assertion that "Excluding this comparator suggests the evidence presented is for interferon ineligible patients only".

AbbVie acknowledges that peg-IFN + RBV was considered a relevant comparator across all subgroups during the appraisal of SOF/VEL. However, the guidance following the appraisal of TA430 recommended SOF/VEL as a treatment for all patient subgroups, regardless of IFN-eligibility, except for the GT2 TN NC subgroup, in which SOF/VEL was only recommended for IFN-ineligible patients. In light of the fact that SOF/VEL shows higher efficacy compared to peg-IFN + RBV, and it is an IFN/RBV-free treatment option, AbbVie expects that there will be no patients receiving peg-IFN + RBV across any genotype and subgroup in which SOF/VEL is recommended by NICE. This is in line with commissioner estimates based on current notification trends in 2016/2017 as reported in the TA430 RIT, where **NICE predicted no use of peg-IFN + RBV** in any genotype. The TA430 RIT is consistent with the June 2017 BASL guidelines, which do not recommend peg-IFN + RBV for any patient subgroup. Furthermore, peg-IFN + RBV alone is listed as a treatment option only for GT2 TN NC IFN-eligible patients in the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1). Therefore peg-IFN + RBV is not a relevant comparator for any subgroup except possibly GT2 TN NC IFN-eligible patients: the submission did consider peg-IFN + RBV as a comparator for IFN-eligible GT2 TN NC patients. Also the EASL guidelines 2016 state: "*from 2016 and onwards, IFN-free regimens are the best options in treatment-naïve and treatment-experienced, DAA-naïve patients with compensated and decompensated liver disease, because of their virological efficacy, ease of use and tolerability*". (EASL guidelines 2016, J Hepatol. 2017 Jan;66(1):153-194).

To reiterate, the evidence (including the choice of comparators) presented in the submission is relevant for all patients regardless of their IFN-eligibility.

Sofosbuvir in combination with ribavirin, with or without peginterferon alfa (for specific people with genotypes 1–6; as recommended by NICE)

This comparator was not considered relevant for GT1 or GT4 because it is not used in clinical practice in England for GT1 and GT4 patients. This is supported by the resource use predictions in the TA430 RIT, expert clinical opinion and the absence of this treatment as a recommended option for patients with GT1 and GT4 infection in the June 2017 BASL guidelines and the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1).

A34

Ongoing studies are listed in section B2.12 , page 135 of the company submission

- Please clarify whether further details are currently available from these studies.
- Please provide timelines and dates for when the results from these studies will be available.
- Please also clarify whether further analyses are planned for any of the glecaprevir-pibrentasvir trials included in the company submission.

Company response:

- All studies are still ongoing and no further details are available at the moment.
- Estimated timelines are as described in clinicaltrials.gov : please see the table below for estimated dates of data availability.

Study	Estimated study completion date	Estimated first date available (*based on internal information or estimated primary completion date*)
M13-576 Long term outcome study	Jan 2020	[redacted]
M16-123 Paediatric study	May 2022	[redacted]
M15-942 Retreatment study (MAGELLAN-3)	Sep 2019	[redacted]
M16-133 NC study	July 2018	[redacted]
M16-135 CC study	Oct 2018	[redacted]
M16-126 G/P in GT5 and 6.	Oct 2018	[redacted]
M16-127	April 208	[redacted]

Regarding further analysis of G/P data in available trials[redacted]

	[redacted]
B1	In the company submission, GT1 patients are not divided into GT1a and GT1b subgroups because of the same treatment duration and similarity of treatment response for the glecaprevir-pibrentasvir GT1a and GT1b subgroups. However, in some NICE technology appraisals there were differences in clinical effectiveness for comparator technologies (for example in TA413) by GT1a and GT1b subgroup, which would result in differential comparative effectiveness. Therefore, consider exploring analyses for GT1a and GT1b subgroups or provide justification why this may not be appropriate. **Company response:** It was considered most appropriate to consider the clinical effectiveness of treatments in the GT1 group as a whole because: ▪ There is no difference in terms of treatment approach or treatment outcomes for GT1a versus GT1b patients with G/P treatment. In an integrated efficacy analysis of G/P in seven phase 2 and 3 trials, no differences were found in SVR12 rates between patients with GT1a and GT1b in patients without cirrhosis. (Puoti et al, EASL 2017, poster SAT-233). Patients with GT1a achieved 99% SVR12 (175/176) and patients with GT1b 100% SVR12 (208/208) following 8 week treatment. The integrated analysis was based on genotype 1 data from ENDURANCE-1 and SURVEYOR-I, part 2. The SVR12 rate in compensated cirrhotic GT1 patients in EXPEDITION- 1 was 99% (89/90). In this cohort there were 48 (33%) GT1a and 39(27%) GT1b patients. One GT1a patient relapsed at post treatment week eight. Taken together these data show that no difference in response to G/P was seen between GT1a and GT1b. This is in line with other products such as e.g. Sovaldi, Harvoni and Epclusa. ▪ This approach is in line with the base-case of the manufacturers' submissions in TA365 and TA364, and the ERG's base-case for the most recent appraisal of a DAA regimen in CHC (TA430). The economic model also already captures the differences in clinical effectiveness for comparator technologies in GT1a and GT1b subgroups in the combined GT1 group. SVR rates for comparators derived from separate GT1a and GT1b populations were used whenever such granular data were available. In such instances, the overall SVR rate for the comparator in GT1 patients is an average of these GT1a- and GT1b-specific SVR rates, weighted by the proportion of GT1a and GT1b subtypes within the GT1 population in the model. When the treatment duration or the requirement for RBV are different for a comparator in GT1a versus GT1b patients, as with OBV/PTV/RTV + DSV, the GT1a- and GT1b-specific SVR rates corresponded to the recommended treatment duration and combination for each subtype.
B2	Baseline patient population characteristics were presented in Tables 61 and 62 on page 151 of the company submission. Please clarify whether these characteristics are the same for all genotypes **Company response:** Baseline patient population characteristics were the same for all genotypes. Please accept our apologies that this was not clear in the submission.
B3	The subgroups listed below were included in the NICE final scope. Please reconsider whether it would be useful to provide cost effectiveness analysis for these subgroups or provide further justification why this may not be appropriate (other than these analyses were not provided in previous hepatitis C submissions. • Co-infection with HIV (in TA430 it was discussed that disease progression might be faster) • Previous treatment received (with DAA or without DAA) • People who have received treatment before liver transplantation • Response to previous treatment • With and without renal impairment • Ineligible/intolerant for interferon treatment (not only for GT2) **Company response:**

	As per the responses to questions A20 and A21, it was not considered feasible to perform subgroup analyses in these special patient populations given the high number of primary subgroups stratified by genotype, cirrhosis status and treatment history, the reduction in statistical power caused by further stratification, and the requirement for comparator data stratified according to these criteria. Notably, during the decision problem meeting, AbbVie understood that the ERG discussed that such an approach to rationalising subgroups would be appropriate. It is also in line with the final scope, which specified that these subgroups may be considered *only if evidence allows*. Regarding previous treatment received and IFN-eligibility: For the proposed subgroup analysis stratifying patients by previous treatment received (with DAA or without DAA), it should be noted that G/P is currently not licensed for patients who have previously failed a prior regimen containing an NS5A- and/or an NS3/4A-inhibitor. The only DAA that TE patients may have failed in order to fall within the licensed population for G/P is SOF, and treatment recommendations for G/P in TE patients are the same regardless of previous treatment received. The TE population considered in the economic model is in line with the licence and defined according to the eligibility criteria of the key phase III trials in the clinical trial programme. Therefore this subgroup analysis has a very limited scope and is not relevant to the decision problem. Considering subgroups defined by IFN-eligibility in genotypes other than GT2 (GT1, GT3–6), as described in the response to question A33, following the introduction of SOF/VEL, IFN-eligibility is not a clinically relevant consideration for treatment recommendations except for GT2 TN NC patients. Peg-IFN + RBV is no longer a relevant comparator for GT1, 3–6, as evidenced by its absence in the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1) in these patient subgroups; it should also be noted that in the TA430 RIT the NICE analysts predicted no use of peg-IFN + RBV, even in GT2 and the TA430 RIT is consistent with the June 2017 BASL guidelines, which do not recommend peg-IFN + RBV for any patient subgroup.

abbvie

B4	**Priority question**: Please consider the following issues and incorporate each of the suggested changes individually and simultaneously in exploratory scenario analyses. Please provide the results for all subgroups (also please provide the new model with the functionality of conducting these suggested exploratory analyses). • In the company submission report, it is not clear whether patients were allowed to die or to transit to more advanced disease stages during the on-treatment period. (i) Please clarify the underlying assumptions and confirm that background mortality was incorporated during the on-treatment period in the company base-case. (ii) If not already incorporated, please explore the impact of disease progression during the on-treatment period as well. • There have been reports of spontaneous remissions of chronic HCV infection in ~3% to 10% of individuals (Thomas et al 2000, JAMA; Watanabe et al 2003, J Med Virol).1, 2 Please incorporate the impact of spontaneous remission (i.e. a positive transition probability from F0 HCV to no HCV in the economic model) • In low-risk patients, there is clear evidence of late relapse occurring post-SVR, together with published estimated rates of late relapse (e.g. Simmons et al 2016, Clin Infect Dis; Klag et al 2017, J Hepatol).3, 4 Please incorporate the reactivation of disease in the economic model, in such a way that a patient who achieved SVR, should return back to his/her pre-SVR fibrosis stage after the disease reactivation. • Please provide a qualitative impact analysis of incorporating onward transmission (with and without re-infection) in the model by explaining the expected model outcomes step by step. **Company response:** **Mortality and disease progression during the on-treatment period** Background mortality was not incorporated during the on-treatment period in the base-case, and patients were not allowed to transit to more advanced disease stages during this period. AbbVie acknowledges that these assumptions introduce a time bias in the model. However, these assumptions are consistent with the economic models provided in several previous appraisals: TA330, TA363 and notably the most recent appraisal, TA430. It may also be noted that the SVR inputs implicitly account for the effect of mortality during the treatment period on the observed treatment success rate and that the introduction of mortality risk would risk double-counting. Furthermore, omitting disease progression during treatment favours those treatments with longer treatment durations and is thus conservative with respect to the present appraisal. During the appraisal of TA363 the ERG acknowledged that the size of the bias and the resultant effect on cost-effectiveness was 'likely to be small,' particularly as these transitions are limited to only a few weeks in the context of a lifetime time horizon. Incorporating these transitions would require substantial structural changes to the model; because these changes are not expected to change the overall direction of the results, these elements have not been incorporated into the model. **Spontaneous remission** Approximately 15–25% of patients with acute HCV infection clear the virus spontaneously. Chronic HCV infection is defined as HCV infection that has not spontaneously cleared after 6 months (Chen et al. 2006), and this was the patient population for the economic model in this submission. AbbVie acknowledges that the two references cited (Thomas et al. 2000 and Watanabe et al. 2003) describe rates of spontaneous remission of 3–10% in

individuals with chronic HCV infection. However, in neither study were the eligibility criteria of the enrolled population defined in accordance with the current accepted definition of CHC: persistent HCV infection that has not spontaneously cleared after 6 months. Furthermore, in these relatively old studies, patients were followed for many years (61-92 months in African Americans in Thomas et al and 7.2 ±2.4 years in Japanese patients in Watanabe et al). These patient cohorts and inclusion criteria were different from the ones used for the G/P clinical studies (e.g. different ethnic populations, HCV infection defined as being anti-HCV antibody positive and previous interferon treatment not allowed). Therefore the applicability of these studies as inputs for spontaneous remission in this economic model is uncertain and would introduce further bias to the modelling.

Of note is that a clearance rate of 3-10% over many years is low compared to the high >90% SVR rates associated with oral DAA therapies, and given the risk of progression to advanced cirrhosis and decompensated cirrhosis with the associated risks of mortality and morbidity, it would be considered clinically unacceptable and against the EASL guidelines (EASL guidelines 2016, J Hepatol. 2017 Jan;66(1):153-194) to wait for several years to see if spontaneous clearance occurs. There is no mention of waiting for spontaneous remission in the EASL guidelines for chronic HCV patients but it is mentioned that patients with acute hepatitis should be considered for antiviral therapy in order to prevent progression to chronic hepatitis. The WHO strategy for elimination of HCV by 2030 is focused on increasing the number of people being tested and treated to reduce new cases of infection and reduce deaths due to HCV infection and there is no mention of spontaneous clearance of chronic HCV being a factor to reach this goal.

Nevertheless, the impact of spontaneous remission has been explored in a scenario analysis, using values from Watanabe et al. 2003 and Thomas et al. 2000. It was assumed that only patients with F0 fibrosis were able to spontaneously clear the virus. It should be noted that the percentages reported in these studies were estimated over the entire study follow-up period and do not represent annual probabilities of spontaneous remission. Annual probabilities have been calculated as follows:

- Watanabe et al. 2003: reported incidence of 0.5% per person per year. This number was converted to an annual probability of 0.005. Note that Watanabe reported a 3.7% cumulative incidence (16/435); however, this cumulative incidence was assessed over a follow-up period of 7.2±2.4 years (mean ± SD, range: 1 to 10 years).
- Thomas et al. 2000: reported a cumulative incidence of 9.79% (90/919) with a median follow-up time of 85 months [IQ range 61-92 months]. Using the 85 months to convert the cumulative incidence rate into an annual probability yields 0.0144.

The scenario analysis was performed in one example subgroup, GT1 TN NC using list price for all interventions. The scenario values can be explored in the model by over-writing the base-case model inputs (in the 'Main Model Inputs' sheet) with the scenario inputs and running an incremental scenario analysis with the 'Active Scenario' selected from the drop down menu. Table 1 reports the base-case incremental cost-effectiveness analysis results for GT1 TN NC patients using the original inputs for this submission (this is identical to the table reporting results for this subgroup in Appendix B14 using list prices for all comparators). Table 2 reports the incremental cost-effectiveness analysis results for GT1 TN NC patients using an annual probability of spontaneous remission of 0.005, in line with Watanabe et al. 2003. Table 3 reports the incremental cost-effectiveness analysis results for GT1 TN NC patients using an annual probability of spontaneous remission of 0.0144, in line with Thomas et al. 2000.

Using a non-zero value for spontaneous remission results in slightly lower costs and slightly higher QALYs for active treatments and no treatment. Using the values for spontaneous remission (from Thomas et al. 2000) G/P is still the cost-effective treatment, with all other treatments dominated by G/P. With the Watanabe value the ICER of G/P versus no treatment is £2,289 per QALY gained, and with the Thomas value the ICER is £2,379 per QALY gained (versus £2,239 per QALY gained in the base-case). Overall, the change in the results is minor.

Table 1: List price base-case incremental cost-effectiveness analysis results for GT1 TN NC patients assuming no spontaneous remission

Technologies	Total costs	Total	Total	Incremental	Incremental	Incremental	ICER versus baseline	ICER incremental

	(£)	LYG	QALYs	costs (£)	LYG	QALYs	(£/QALY)	(£/QALY)
No treatment	19,514	18.77	12.66	NA	NA	NA	NA	NA
G/P	27,657	20.40	16.30	8,143	1.633	3.638	2,239	2,239
SOF/LDV	28,437	20.34	16.15	8,922	1.565	3.488	2,558	Dominated
OBV/PTV/RTV + DSV	37,718	20.38	16.23	18,204	1.603	3.567	5,103	Dominated
EBR/GZR	39,224	20.31	16.08	19,710	1.537	3.421	5,761	Dominated
SOF/VEL	40,860	20.39	16.28	21,346	1.623	3.619	5,899	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 2: List price incremental cost-effectiveness analysis results for GT1 TN NC patients with Watanabe et al. 2003 spontaneous remission data

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No treatment	19,390	18.78	12.69	NA	NA	NA	NA	NA
G/P	27,656	20.40	16.30	8,266	1.627	3.611	2,289	2,289
SOF/LDV	28,431	20.34	16.15	9,041	1.559	3.463	2,611	Dominated
OBV/PTV/RTV + DSV	37,715	20.38	16.23	18,325	1.598	3.541	5,175	Dominated
EBR/GZR	39,216	20.31	16.08	19,826	1.532	3.397	5,837	Dominated
SOF/VEL	40,858	20.39	16.28	21,468	1.617	3.592	5,976	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 3: List price incremental cost-effectiveness analysis results for GT1 TN NC patients with Thomas et al. 2000 spontaneous remission data

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No treatment	19,171	18.79	12.73	NA	NA	NA	NA	NA

G/P	27,654	20.41	16.30	8,483	1.617	3.565	2,379	2,379
SOF/LDV	28,420	20.34	16.15	9,249	1.549	3.418	2,706	Dominated
OBV/PTV/RTV + DSV	37,709	20.38	16.23	18,538	1.587	3.496	5,303	Dominated
EBR/GZR	39,201	20.31	16.09	20,030	1.522	3.353	5,974	Dominated
SOF/VEL	40,855	20.40	16.28	21,684	1.607	3.546	6,114	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Finally, it should be noted that clinical opinion generally supports the base-case modelling assumption that the rate of spontaneous remission in CHC is 0 (Hartwell et al. 2011), and this assumption is consistent with the base-case of previous NICE TAs, including the recent appraisal of the pan-genotypic regimen SOF/VEL (TA430).

Re-infection

As described in B.3.2.2.4 (p. 145) of the submission, re-infection was not incorporated into the model due to the infeasibility of incorporating onward transmission into the current modelling framework.

The NICE Committee's discussion in the appraisal of TA430 acknowledged that 'excluding reinfection may overestimate the health benefits of more effective treatments.' However, the Committee also agreed that 'without a model that incorporated both reinfection and transmission, cost-effectiveness results excluding reinfection and transmission were acceptable for its decision making.' This is because re-infection and onward transmission prevention have opposing effects on the cost-effectiveness of treatments calculated by the model.

Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, with that risk being a function of the number of infectious individuals in the population (Pitman et al. 2012). Such a dynamic model would allow one to model the benefits of onward transmission prevention offered by highly effective treatments that are not captured with the current model structure. Given that onward transmission could not be incorporated into the current modelling framework, the approach was taken to exclude re-infection and onward transmission from the model in the base-case, in line with the Committee's discussion in TA430.

Nevertheless, the impact of viral re-infection has been explored in a scenario analysis. To explore the impact of a high re-infection value, an annual reinfection probability of 0.0033 was used, which is the upper 95% confidence interval of the value for recurrence of late relapse/reinfection of HCV from Simmons et al. 2016 Clin Infect Dis. The scenario value can be explored in the model by over-writing the base-case model input (in the 'Main Model Inputs' sheet) with the scenario input and running an incremental scenario analysis with the 'Active Scenario' selected from the drop down menu.

The scenario analysis was performed in one example subgroup, GT1 TN NC using list price for all interventions. Table 4 reports the base-case incremental cost-effectiveness analysis results for GT1 TN NC patients using the original inputs for this submission (this is identical to the table reporting results for this subgroup in Appendix B14 using list prices for all comparators). Table 5 reports the incremental cost-effectiveness analysis results for GT1 TN NC patients using an annual probability of viral re-infection of 0.0033.

Using a non-zero value for viral re-infection results in slightly higher costs and slightly lower QALYs for active treatments. G/P is still the cost-effective treatment, with all other treatments dominated by G/P; the ICER of G/P versus no treatment is £2,538 per QALY gained (versus £2,239 per QALY gained in the base-case).

Table 4: List price base-case incremental cost-effectiveness analysis results for GT1 TN NC patients assuming no viral re-infection

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No treatment	19,514	18.77	12.66	NA	NA	NA	NA	NA
G/P	27,657	20.40	16.30	8,143	1.633	3.638	2,239	2,239
SOF/LDV	28,437	20.34	16.15	8,922	1.565	3.488	2,558	Dominated
OBV/PTV/RTV + DSV	37,718	20.38	16.23	18,204	1.603	3.567	5,103	Dominated
EBR/GZR	39,224	20.31	16.08	19,710	1.537	3.421	5,761	Dominated
SOF/VEL	40,860	20.39	16.28	21,346	1.623	3.619	5,899	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 5: List price incremental cost-effectiveness analysis results for GT1 TN NC patients assuming non-zero viral re-infection

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No treatment	19,514	18.77	12.66	NA	NA	NA	NA	NA
G/P	28,387	20.36	16.16	8,873	1.587	3.496	2,538	2,538
SOF/LDV	29,137	20.29	16.01	9,622	1.521	3.352	2,871	Dominated
OBV/PTV/RTV + DSV	38,435	20.33	16.09	18,921	1.558	3.428	5,520	Dominated
EBR/GZR	39,912	20.27	15.95	20,397	1.494	3.288	6,204	Dominated
SOF/VEL	41,586	20.35	16.14	22,072	1.577	3.478	6,347	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

	Qualitative impact of incorporating onward transmission The inclusion of the prevention of onward transmission would likely result in a lower ICER for all active treatments, particularly those that are most effective. Assuming that the rate of re-infection is 0, patients who achieve SVR will not spread HCV infection to others. Therefore, one effect of treatment on wider society would be to reduce onward transmission, which in turn reduces the prevalence and incidence of CHC. The result would be reduced healthcare costs associated with CHC (i.e. lower costs), and lower morbidity and mortality associated with CHC (i.e. higher QALYs). As discussed previously, re-infection and the prevention of onward transmission have opposing effects on the cost-effectiveness of treatments. As such, compared to a model that incorporates the prevention onward transmission but not re-infection, a model that incorporates both re-infection and the prevention of onward transmission will result in higher ICERs for all active treatments. However, Madin-Warburton et al. (2016) recently showed that in a dynamic transmission model for treatment of HCV infection that incorporates both re-infection and onward transmission, the effects of reducing onward transmission outweigh the effects of re-infection, resulting in a net positive impact on the cost-effectiveness of treatment. Therefore, the Markov model presented in this submission may represent a conservative approach that under-estimates the cost-effectiveness of active treatments including G/P.

B5	**Priority question:** If questions A28, A29, A32 and A33 lead to any updates of the data (e.g. by including other available non-randomized observational clinical studies), please provide an updated model including these data and provide all new results. **Company response:** Answers provided to questions A28, A29, A32, and A33 do not require a model update.
B6	There are some minor inconsistencies between the datasets used for SVR rates and AE rates, for example in Table 65 on page 158, for GT3 TN NC SOF/VEL SVR is taken from ASTRAL-3, but in Table 68, the AE rate for the same subgroup was from pooled data from ASTRAL-3 and POLARIS-3 studies. Please check and confirm that the same datasets were used for deriving SVR rates and AE rates; if there are exceptions, either explain the reason or alter the input to achieve consistency. **Company response:** GT3 TN NC SOF/VEL: • SVR in Table 65 was reported incorrectly. In the model, data extracted from ASTRAL-3 and POLARIS-3 were combined = 98.2% (please also see response to A28) • AE from Table 68 is correct: ○ Anaemia = 0.00% ○ Rash = 0.00% ○ Depression = 0.00% ○ Neutropenia = 0.26% ○ Thrombocytopenia = 0.52%
B7	The costs of five adverse events were incorporated into the economic model (anaemia, rash depression, grade ¾ neutropenia and depression). Please provide further clarification of the criteria for selecting adverse events in the economic model **Company response:** Adverse events (AEs) of relevance were considered by reviewing previous NICE appraisals in the therapy area, particularly the most recent appraisal of the pan-genotypic treatment SOF/VEL (TA430). Compared to the AEs included in TA430, only nausea, vomiting, diarrhoea and pruritus were excluded from the economic model in this submission. These AEs were excluded because the cost of these events is very small and thus has minimal impact on the cost-effectiveness estimates. This simplifying approach was also pragmatic given the number of subgroups and comparators considered in the submission.
B8	The expected treatment duration calculation appears to be based on an assumption that patients discontinue treatment at the midpoint of the licensed treatment duration. ▪ Please provide the median time to treatment discontinuation for all treatments for each subgroup ▪ Please provide the results of the scenario analysis (as facilitated by the dropdown box on sheet 'main model input' cell H38) in which it is assumed that each treatment was administered during the whole licensed treatment duration. **Company response:** **Median time to treatment discontinuation** The median time to treatment discontinuation was not available for all comparators in the referenced sources. However, in most cases, it is safe to assume that the median treatment duration time correspond to the full treatment course because the number of patients' discontinuing treatment is negligible with the G/P and most model comparators. **Administration of each treatment for the whole licensed duration** The expected treatment duration in the model for all subgroups receiving 12 weeks of treatment with G/P is 84.0 days (12 weeks exactly), and 112.0 (16 weeks exactly) for all subgroups receiving 16

	weeks of G/P; consequently, all patients in these subgroups are already modelled to incur the full cost of treatment. The expected treatment duration for all subgroups receiving 8 weeks of treatment is 55.5 days to 56.0 days (56.0 days is 8 weeks exactly), so these are the only subgroups affected. Given the small number of patients affected and the marginal increase of at most one half of the daily cost of treatment per patient, the increase in cost for G/P that would result from applying the full course cost for these patients is expected to be so minor as to not affect the overall direct of the results in these subgroups. AbbVie acknowledges that the pricing scenario analysis could be adjusted such that the full costs of an opened package of comparator treatments is incurred, even if the whole package was not consumed. The effect of this would be to increase the costs associated with comparator treatments [redacted]. Because the requested scenario analysis would increase the costs associated with comparator treatments (but not G/P), [redacted] [redacted] [redacted]

abbvie

B9

For the Fibrosis progression, please use the alternative transition probabilities from Grischenko et al 2009 (together with Kanwal HRs for GTs) instead of Thien 2009 in a scenario analysis (as in TA413).

Company response:
We were aware that ERG requested Grishchenko et al. fibrosis progression probabilities as a sensitivity in TA413 in Scenario 3. In Scenario 3, the age-dependent transition probabilities from Grishchenko mild to moderate and moderate to cirrhosis where applied to the model submitted for elbasvir-grazoprevir which relied on a structure with METAVIR stages. Specifically, the transition probabilities for mild to moderate were applied for the transition between F0 to F1, F1 to F2 and F2 to F3, and the transition probabilities for moderate to cirrhosis where applied to the transition probabilities for F3 to F4 (see Table 5.29 in TA413.)

Therefore, we had previously included these transition probabilities into the model. However, we concluded that the fibrosis progression probabilities from Grishchenko et al. 2009 are not appropriate in a model structure with METAVIR stages as implemented in Scenario 3 of TA413.

The reason is that using these probabilities in a model with METAVIR stages will severely under predict cumulative incidence of patient's reaching cirrhosis after 20 years. As an example, assuming a cohort of untreated patients with METAVIR stage F0 in GT1 treatment-naïve, using Grishchenko transition probabilities the model predicts that 0.4% of these patients will reach cirrhosis in a 20-year period, this is significantly less than the prediction generated by the model when using Thein transition probabilities which is 21.3%. The prediction obtained using Thein aligns with the findings in the literature.

Source	20-year proportion of cases with cirrhosis
Model using Grishchenko et al. 2009	0.4%
Model using Thein et al. 2009	21.3%
Freeman et al. 2001. Liver clinics	21.9%
Freeman et al. 2001. Community	6.5%
Thein et al. 2008	20.0%
Alter et al. 2000	18.0%
Seeff, 2009	16.0%
Brady et al. 2007	19.0%

Nevertheless, results are provided using the Grishchenko transition probabilities for one example subgroup, GT1 TN NC, using list price for all interventions. The transition probabilities are reported in Table 6. The scenario values can be explored in the model by over-writing the base-case model inputs (in the 'Main Model Inputs' sheet) with the scenario inputs and running an incremental scenario analysis with the 'Active Scenario' selected from the drop down menu.

Table 6: Grishchenko transition probability inputs

	Age at Treatment		
GT1 TPs	**30 Years**	**40 Years**	**50 Years**

F0 to F1	0.015	0.023	0.035
F1 to F2	0.015	0.023	0.035
F2 to F3	0.015	0.023	0.035
F3 to F4	0.021	0.032	0.048
Non-GT1 TPs			
F0 to F1	0.022	0.033	0.049
F1 to F2	0.022	0.033	0.049
F2 to F3	0.022	0.033	0.049
F3 to F4	0.030	0.046	0.069

Table 7 reports the base-case incremental cost-effectiveness analysis results for GT1 TN NC patients using the original inputs for this submission (this is identical to the table reporting results for this subgroup in Appendix B14 using list prices for all comparators). Table 8 reports the incremental cost-effectiveness analysis results for GT1 TN NC patients using the Grishchenko inputs. Using the Grishchenko inputs results in slightly lower costs and slightly higher QALYs for active treatments, and lower costs and higher QALYs for no treatment. G/P is still the cost-effective treatment, with all other treatments dominated by G/P; the ICER of G/P versus no treatment is £11,189 per QALY gained (versus £2,239 in the base-case).

Table 7: List price base-case incremental cost-effectiveness analysis results for GT1 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No treatment	19,514	18.77	12.66	NA	NA	NA	NA	NA
G/P	27,657	20.40	16.30	8,143	1.633	3.638	2,239	2,239
SOF/LDV	28,437	20.34	16.15	8,922	1.565	3.488	2,558	Dominated
OBV/PTV/RTV + DSV	37,718	20.38	16.23	18,204	1.603	3.567	5,103	Dominated
EBR/GZR	39,224	20.31	16.08	19,710	1.537	3.421	5,761	Dominated
SOF/VEL	40,860	20.39	16.28	21,346	1.623	3.619	5,899	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 8: List price incremental cost-effectiveness analysis results for GT1 TN NC patients with Grishchenko inputs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No treatment	8,536	20.18	14.62	NA	NA	NA	NA	NA
G/P	27,552	20.42	16.32	19,016	0.242	1.700	11,189	11,189
SOF/LDV	27,895	20.41	16.25	19,359	0.232	1.628	11,891	Dominated
OBV/PTV/RTV + DSV	37,417	20.41	16.28	28,881	0.238	1.664	17,356	Dominated
EBR/GZR	38,483	20.40	16.21	29,947	0.228	1.597	18,754	Dominated
SOF/VEL	40,688	20.42	16.31	32,152	0.241	1.693	18,996	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

abbvie

B10

Some of the transition probabilities in Table 75, page 178 are different from those used in TA430. .
• For CC to DCC, CC to HCC and DCC to HCC: please justify the choice of Fattovich et al 1997 as the input source, and conduct a scenario analysis using the input from Cardoso et al 2010.
• For LT related death probabilities: please justify the model input used and provide a scenario analysis using the inputs from TA430 (EAP data and Bennet et al.)

Company response:
CC, DCC and HCC transition probabilities
The choice of Fattovich et al. 1997 as the input source for the transition probabilities for CC to DCC, CC to HCC and DCC to HCC is in line with previous TAs including TA413 and TA365. TA430 used Cardoso et al. 2010 as the input source for these transition probabilities. However, in the Committee's discussion of the Gilead's source selection for these inputs, the Committee considered that clinical experts agreed that the data from Fattovich et al. 1997 is generalisable to current practice, justifying its use in the model in this submission. In previous appraisals for CHC treatments the Committee has concluded the then true transition probabilities lie between the values from Fattovich et al. 1997 and the values from Cardoso et al. 2010.

Results are provided using the Cardoso inputs for one example subgroup, GT1 TN NC, using list price for all interventions. The scenario values can be explored in the model by over-writing the base-case model inputs with the scenario inputs (in the 'Main Model Inputs' sheet) and running an incremental scenario analysis with the 'Active Scenario' selected from the drop down menu.

Table 9 reports the base-case incremental cost-effectiveness analysis results for GT1 TN NC patients using the original inputs for this submission (this is identical to the table reporting results for this subgroup in Appendix B14 using list prices for all comparators). Table 10 reports the incremental cost-effectiveness analysis results for GT1 TN NC patients using the Cardoso inputs. All results are at list price for all interventions.

Using the Cardoso inputs results in slightly lower costs and slightly lower QALYs for active treatments and no treatment. G/P is still the cost-effective treatment, with all other treatments dominated by G/P; the ICER of G/P versus no treatment is £2,194 per QALY gained (versus £2,239 per QALY gained in the base-case).

Table 9: List price base-case incremental cost-effectiveness analysis results for GT1 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No treatment	19,514	18.77	12.66	NA	NA	NA	NA	NA
G/P	27,657	20.40	16.30	8,143	1.633	3.638	2,239	2,239
SOF/LDV	28,437	20.34	16.15	8,922	1.565	3.488	2,558	Dominated
OBV/PTV/RTV + DSV	37,718	20.38	16.23	18,204	1.603	3.567	5,103	Dominated

EBR/GZR	39,224	20.31	16.08	19,710	1.537	3.421	5,761	Dominated
SOF/VEL	40,860	20.39	16.28	21,346	1.623	3.619	5,899	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 10: List price incremental cost-effectiveness analysis results for GT1 TN NC patients with Cardoso inputs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No treatment	18,430	17.74	12.09	NA	NA	NA	NA	NA
G/P	27,647	20.40	16.29	9,217	2.654	4.200	2,194	2,194
SOF/LDV	28,381	20.28	16.12	9,951	2.544	4.027	2,471	Dominated
OBV/PTV/RTV + DSV	37,688	20.35	16.21	19,258	2.606	4.119	4,675	Dominated
EBR/GZR	39,151	20.24	16.04	20,721	2.499	3.951	5,244	Dominated
SOF/VEL	40,843	20.38	16.27	22,413	2.638	4.178	5,365	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Liver-related mortality transition probabilities

TA430 use of EAP data (DCC to liver death). The transition probability from DCC or liver death in this submission was sourced from Fattovich et al. 1997, to remain consistent with the use of this source for CC, DCC and HCC transition probabilities as described above. This is also consistent with previous appraisals including TA413 and TA365. In contrast, TA430 used EAP data for the transition from DCC to liver death.

Scenario analysis results are not presented, because scenarios requested in priority questions and in common with ERG queries in previous appraisals for DAA therapies in CHC have been prioritised. However, this scenario can be explored in the model by over-writing the base-case model inputs with the scenario inputs in 'Main Model Inputs' cells Z144 and Z145, and running an incremental scenario analysis with the 'Active Scenario' selected from the drop down menu.

TA430 use of Bennet et al. data (liver transplant to liver death). The transition probabilities from LT (first year) or LT (subsequent year) to liver death in this submission were sourced from Grieve et al. 2006 and Bennett et al. 1997, respectively. The value from Grieve et al. 2006 for the transition from LT (first year) to liver death is consistent with TA365. This choice of input was not discussed by the ERG or the Committee in TA365. The value from Bennett et al. 1997 for the transition from LT (subsequent year) to liver death is

	consistent with several previous NICE appraisals, including TA413, TA365 and TA364. In this respect, TA430 diverged from the precedent of previous appraisals in that the model did not have separate health states for first and subsequent LT years; rather, for the transition from the single LT health state to death a distinct value was used from Bennett et al. 1997 (i.e. not the same as the value used in this submission for LT [subsequent year] to liver death, which was also sourced from Bennett et al. 1997). Scenario analysis results are not presented, because scenarios requested in priority questions and in common with ERG queries in previous appraisals for DAA therapies in CHC have been prioritised. However, this scenario can be explored in the model by over-writing the base-case model inputs with the scenario inputs in 'Main Model Inputs' cells Z144 and Z145, and running an incremental scenario analysis with the 'Active Scenario' selected from the drop down menu.

B11	Please provide the results of the following scenario analyses (with functionalities in the model) individually and simultaneously. • Incorporating the age based utility decrement (using a similar approach to TA413) • Assume no utility gain from SVR • Assuming no treatment related health utility change (also can you please confirm the consistency between the datasets used in Table 78 with the datasets used to derive SVR and AE rates?) • Applying health related disutilities for AEs (for depression please do not forget that it might have impacts in later years). **Company response:** *Age-based utility decrement* The base-case model inputs from Thein et al. are already age-dependent. Incorporating an additional age-based utility decrement would double-count the impact of age on QoL. Therefore this scenario has not been incorporated. *No utility gain from SVR* This scenario can be explored in the model by copying the values from 'Scenario 4' in 'Main Model Inputs' H233:H243 over the corresponding base-case model values in the 'Main Model Inputs' sheet, and running an incremental scenario analysis with 'Active Scenario' selected from the drop down menu. *No treatment-related health utility change* This scenario can be explored in the model by setting the H62 and L62 cell values in the 'Main Model Inputs' sheet to 0, and running an incremental scenario analysis with 'Active Scenario' selected from the drop down menu. *Applying health-related disutilities for AEs* For patients receiving a DAA therapy, to reflect the impact of treatment on utility over the treatment period, patient utility is adjusted in the year of treatment by a treatment-related health utility change value specific to each DAA therapy. These treatment-related health utility changes reflect the overall effect of DAA therapy on patients' HRQoL, and were measured in clinical trials by calculating the change in health utility index score at the end of treatment compared to before treatment. Therefore these values already capture the negative effect of AEs associated with treatment on patients' HRQoL. Adding health-related disutilities for AEs would introduce 'double-counting' of the negative effect of AEs on HRQoL. Therefore this has not been incorporated into the model.
B12	**Priority question:** It is stated in the company submission that the drug costs are charged daily. However an opened package may not be used. Please provide a scenario in which full costs of an opened package is incurred, even if the whole package was not consumed. **Company response:** The ERG agreed on Friday 24th August 2017 that it was appropriate to refer to the response to B8 (second bullet) for this question: The scenario requested here is in practice a duplicate of that requested in the second bullet point of B8. The assumption in the scenario in B8 is that each treatment was administered during the whole licensed treatment duration. The assumption in the scenario in B12 is that the full costs of an opened package are incurred, even if the whole package was not consumed. Because the recommended treatment duration for all interventions corresponds with the complete use of 1 or more packs, with no treatment duration requiring the use of a fraction of a pack, the scenarios are in practice the same.

abbvie

B13

Please provide a scenario analysis in which the inflation adjusted health state costs from TA430 (in Table 82) are used.

Company response:
Table 11 summarises the health state costs used in the base-case of the submission, the values used in TA430, and the values used in the scenario analysis requested. Wherever possible the health state costs from TA430 were used as described in Table 11. This was possible for all inputs except LT (subsequent year). There was limited information in the TA430 regarding the health state cost beyond 24 months after the liver transplant. In light of this uncertainty, the original input used in the submission was retained.

Table 11: Summary of health state costs used in scenario analysis with adjusted health state costs from TA430

Variable	G/P submission base-case value	Source	TA430 value and reference	Value in scenario analysis
Health state costs (2015/2016 £)			**(2014/2015 £)**	
F0	£164	Hartwell et al. (2011)	£327 Calculation: 83%,17% split[a] Wright et al. (2006) Mild: £189 (inflated) Moderate: £1,001 (inflated)	£189
F1	£164			£189
F2	£609	Backx et al. (2014)		£1,001
F3	£609			£1,001
CC	£945		£1,561 Wright et al. (2006)	£1,561
SVR, history of mild fibrosis(F0–F1)	£60	Backx et al. (2014)	£246 Calculation: 83%,17% split[a] Grishchenko et al. (2009) SVR, mild: £237 (inflated) SVR, moderate: £290 (inflated)	£237
SVR, history of moderate fibrosis (F2–F3)	£60			£290
SVR, history of CC	£606		£513 Grishchenko et al. (2009)	£513
DCC	£12,670	Hartwell et al. (2011)	£12,510 Wright et al. (2006)	£12,510
HCC	£11,291		£11,147 Wright et al. (2006)	£11,147
LT (first year)	£51,108		1st year LT: £85,191; 1st year post LT 0-12 months: £28,067; subsequent year £4,194 (12-24 months). From Singh/Longworth et al. (2014); split between post-liver	£85,191
LT (subsequent year)	£1,924			£1,924

			transplant year 1 and year 2 cost based on Wright et al. (2006)	

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

Abbreviations: AE, adverse event; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; SVR, sustained virologic response

The scenario analysis was performed in one example subgroup, GT1 TN NC by over-writing the base-case values (in the 'Main Model Inputs' sheet) with the inputs in Table 11. Results are reported using list price for all interventions. Table 12 reports the base-case incremental cost-effectiveness analysis results for GT1 TN NC patients using the original inputs for this submission (this is identical to the table reporting results for this subgroup in Appendix B14 using list prices for all comparators). Table 13 reports the incremental cost-effectiveness analysis results for GT1 TN NC patients using the values from the TA430 inputs for health state costs ('Value in scenario analysis' described in Table 11). Total and Incremental LYG and QALYs are unchanged for each intervention between Table 12 and Table 13. In the scenario analysis, total costs were higher for no treatment and all active treatments compared to the base-case. Nevertheless, in the scenario analysis and the base-case G/P dominated all active treatments, and was cost-effective versus no treatment. The ICER for G/P versus no treatment was lower in the scenario analysis (£1,819 per QALY gained) compared to in the base-case (£2,239 per QALY gained).

Table 12: List price base-case incremental cost-effectiveness analysis results for GT1 TN NC patients with original health state cost inputs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No treatment	19,514	18.77	12.66	NA	NA	NA	NA	NA
G/P	27,657	20.40	16.30	8,143	1.633	3.638	2,239	2,239
SOF/LDV	28,437	20.34	16.15	8,922	1.565	3.488	2,558	Dominated
OBV/PTV/RTV + DSV	37,718	20.38	16.23	18,204	1.603	3.567	5,103	Dominated
EBR/GZR	39,224	20.31	16.08	19,710	1.537	3.421	5,761	Dominated
SOF/VEL	40,860	20.39	16.28	21,346	1.623	3.619	5,899	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

Table 13: List price base-case incremental cost-effectiveness analysis results for GT1 TN NC patients withTA430 health state cost inputs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No treatment	24,871	18.77	12.66	NA	NA	NA	NA	NA
G/P	31,487	20.40	16.30	6,616	1.633	3.638	1,819	1,819
SOF/LDV	32,331	20.34	16.15	7,459	1.565	3.488	2,139	Dominated
OBV/PTV/RTV + DSV	41,576	20.38	16.23	16,704	1.603	3.567	4,683	Dominated
EBR/GZR	43,144	20.31	16.08	18,272	1.537	3.421	5,341	Dominated
SOF/VEL	44,700	20.39	16.28	19,828	1.623	3.619	5,480	Dominated

Abbreviations: DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GZR, grazoprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life-years gained; N/A, not applicable; NC, non-cirrhotic; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; RTV, ritonavir; SOF, sofosbuvir; TN, treatment-naïve; VEL, velpatasvir

B14	**Priority question:** The results as presented in the company submission (document B) appear not to match the base-case results found in the electronic model. Please explain if certain settings in the model should be changed in order to reproduce the results in B.3.7 or if the results in B.3.7 are not based on the submitted electronic model. **Company response:** AbbVie can confirm that the settings in the model provided to NICE are correct and aligned with the model inputs described in the submission. The base-case results in the submission, which do not match the results from the model AbbVie provided to NICE, were taken from an earlier iteration of the model in error. AbbVie has provided the following updated results in Appendix B14, which are aligned with the results of the model provided to NICE: • Updated base-case results (in place of those described in Section B.3.7 starting on p. 201, using the list price for all treatments) • Updated PSA analysis results (in place of those described in B.3.8.1.2 starting on p. 217) • Updated DSA analysis results (in place of those described in B.3.8.2.2 on p. 218, and in place of the tornado diagrams presented in Appendix L.1.3) • Updated price scenario analysis results (in place of those described in B.3.7.3.2 on starting on p. 220, and in place of those reported in Appendix L.1.4) [redacted] [redacted]
B15	The first scenario analysis (as described in section B.3.8.3) appears not to be fully implemented in the economic model. Instead, only step two of the changes made [redacted] appears to be implemented in a macro. Please confirm that step 1 and 3, i.e. changes in the [redacted] and the price for OBV/PTV/RTV ± DSV need to be implemented manually. If this is indeed the case, please provide an updated macro that makes these changes automatically when running the macro. **Company response:** [redacted] leaving this functionality open allows flexibility to adjust prices for other comparators in the case they have a PAS or CMU price.
B16	Please include the parameter 'treatment monitoring costs' in both the PSA and the DSA. **Company response:** The updated model includes treatment monitoring costs in the DSA and PSA. The treatment monitoring costs low and high values were set to ± 50%. The treatment monitoring costs were assumed to follow a gamma distribution. The standard deviation for each treatment monitoring cost was calibrated, using replications of 500 random draw, such that the 95% confidence interval would correspond to the assumed model low and high values.
B17	Please provide the list of technical /internal validation tests conducted (section B.3.10.1 of the company submission). **Company response:** This is now provided in Appendix B17
B18	**Priority question**: Please consider conducting a cross-validation of the results for each sub-group by comparing the total life years, quality adjusted life years and costs for each comparator in the model with those in the models for previous assessments (e.g. TA430 and TA413). **Company response:** The overall costs associated with CHC treatments in economic models are driven primarily by the

cost of treatment. This is evident from this submission when comparing the results of the base-case analysis to the results of the pricing scenario analysis, in which the only parameter that was varied was the price of G/P. Due to the fact that various comparators considered in this submission have confidential pricing agreements, analyses using treatment list prices (which are invariant across submissions) do not reflect costs used in actual practice. It was therefore not considered relevant to perform a cross-validation of the costs for each comparator in the model with previous assessments. Thus, AbbVie considered to undertake a cross-validation of QALYs and LYG only.

In light of the large number of comparators and subgroups presented in this submission, AbbVie has taken the pragmatic approach of cross-validating the results for SOF/VEL in TA430 in GT1 and GT3 TN NC subgroups only (Table 14). SOF/VEL was selected as it is the only pan-genotypic comparator treatment; GT1 and GT3 were selected because these are the most prevalent strains in the UK; TN NC patients were selected because the majority of patients with CHC are TN NC.

The values for SOF/VEL from TA430 were sourced from Section 5.7.2 of the company submission ('Base-case incremental cost effectiveness analysis results'). QALYs for SOF/VEL in this submission were taken from the updated base-case results provided in Appendix B14.

As shown in Table 14, when cross-comparisons were possible due to the absence of redaction in TA430, QALYs and LYG calculated for SOF/VEL in this submission were within ~7% of those in TA430. Given that the SVR12 rate inputs for SOF/VEL between TA430 and this submission were identical for both subgroups (Table 14), this small difference likely reflects the differences in the model structure, and is not driven by an underestimation of the effectiveness of SOF/VEL in achieving SVR12 in this submission.

Table 14: Cross-validation of SOF/VEL QALYs and LYGs from TA430 and this submission

	QALYs		LYG		SOF/VEL SVR12 rate	
	TA430	G/P submission	TA430	G/P submission	TA430	G/P submission
GT1 TN NC	17.27	[redacted]	21.86	[redacted]	98.4%	98.4%
GT3 TN NC	XX	[redacted]	21.84	[redacted]	98.2%	98.2%

Abbreviations: CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; LYG, life years gained; NC, non-cirrhotic; QALY, quality-adjusted life year; SOF/VEL, sofosbuvir/ledipasvir; SVR, sustained virologic response; TA, technology appraisal; TN, treatment-naïve; XX, value redacted in company submission

B19

Please provide a scenario analysis using all inputs and assumptions in line with the TA430. Provide the results of glecaprevir-pibrentasvir and compare the LY, QALY and cost results of PR, BSC and SOF/VEL with the reported results in TA430.

Company response:
This scenario analysis requires extensive changes to the base-case model inputs. Because scenario analyses using specific TA430 inputs have been provided in responses to prior questions, this scenario analysis has not been completed.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Glecaprevir with pibrentasvir for treating chronic hepatitis C [ID1085]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The Hepatitis C Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The national patient charity for people living with or affected by hepatitis C funded by grant-making trusts, individual donations, some government grants and grants from industry. We have over 3,000 members of our patient association.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Through our national helpline and our work on the ground through our peer community and prison projects and our outreach service
Living with the condition	
6. What is it like to live with the condition? What do carers	This varies. Some people experience few if any symptoms, while others can be so debilitated that they cannot work and find much of their social/emotional/sexual life significantly impaired (by for example

experience when caring for someone with the condition?	chronic fatigue, mood swings and sexual dysfunction). Equally some people encounter stigma (because of the association with drug use usually) and even discrimination, including loss of job. People who were infected through the NHS often feel extremely angry and bitter because they feel the government has never accepted responsibility or adequately compensated them. In some parts of the country people living with hepatitis C are currently experiencing significant uncertainty about when they will have access to interferon-free therapy and hence a cure because NHS England has introduced a cap on the number to be treated in 2017/18. The experience for carers varies in the same way, depending how symptomatic the patient is. For carers one of the most difficult issues is when treatment does not work or the patient is diagnosed too late and develops liver cancer. Good treatments for liver cancer do not exist and unless it is caught early enough for resection or transplantation, it is generally fatal within months.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	They are generally happy that interferon-free treatment is available for everyone except those with genotype 2. They are not happy that the only treatment available is whatever is cheapest that month, rather than the best for them. They are not happy they cannot be retreated if treatment does not work, especially if they were not allowed the best option initially. Those having to wait for treatment want to know why people with hepatitis C are singled out for rationing and believe it is only because of the stigma of hepatitis C. They are not happy that NICE has allowed this to happen.
8. Is there an unmet need for patients with this condition?	Yes. People with genotype 2 who are not interferon intolerant. People needing retreatment. Treatment for people rarely in touch with services who need to be treated immediately in case they are not in touch with services again for a long time (e.g. PWID, people in prison) but who are denied because of rationing.

	Competitor drugs to the current pan-genotypic regime in order to drive down prices enough to persuade NHSE to stop rationing treatment. This should not be a consideration but in the 'make-it-up-as-we-go-along' world of guidance for hepatitis C, where NICE issues ambiguous guidance, NHSE uses NICE's costing template as a rationing cap and price is the determinant of treatment selection, it is.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	That it has very high cure rates That it offers retreatment options That it offers competition to Epclusa and therefore may allow the removal of rationing
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None of significance

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**

Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- This could end completely the use of interferon which can cause significant long-term harm
- This could offer an option for retreatment
- This could drive down the price of drugs allowing NHSE to remove rationing
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Glecaprevir with pibrentasvir for treating chronic hepatitis C [ID1085]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Society of Gastroenterology : liver section**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	✓ ☐ an employee or representative of a healthcare professional organisation that represents clinicians? ✓ ☐ a specialist in the treatment of people with this condition? ✓ ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Society of Gastroenterology is an organisation focused on the promotion of gastroenterology within the United Kingdom. It has over three thousand members drawn from the ranks of physicians, surgeons, pathologists, radiologists, scientists, nurses, dietitians, and others interested in the field. Founded in 1937 it has grown from a club to be a major force in British medicine, with representation within the British Royal Colleges and consequently the Department of Health and Government. Internationally it is represented at World and European level. The BSG is a registered charity. It is funded by subscription from members.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility,	The goal of therapy is to cure hepatitis C virus (HCV) infection to prevent progressive hepatic fibrosis and eventual cirrhosis with subsequent symptomatic (decompensation) cirrhosis, hepatoma development , severe extrahepatic manifestations and death .

to cure the condition, or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The endpoint of therapy is undetectable HCV RNA in blood (lower limit of detection ≤15 IU/ml) at 12 weeks known as sustained virological response (SVR 12). In patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, the risk of hepatocellular cancer.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Urgent need: • Effective re-treatment options for all HCV genotypes treatment failures with previous DAA (particularly NS5A inhibitor) exposure. Those individuals exposed to NS5A inhibitors represent the majority of recent treatment failures and may have long lasting resistance associated substitutions (RAS) in HCV viral population. Although treatment failure is rare, numerically in England, due to the large existing disease burden, these patients will represent a substantial population. • Pangenotypic therapy for patients with advanced chronic kidney disease (eGFR <30ml/mim) – the only regimes currently available are for HCV G1 & 4 • Shorter treatment regimens - particularly for special groups eg.Prison population • Pangenotypic therapy • Ribavirin (RBV) free treatment regimes to minimise side effects of treatment

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients are treated via regional HCV operational delivery networks (ODNs). Individual cases are discussed at local HCV multi-disciplinary meetings (MDM) with a decision to treat HCV on criteria of disease severity (to prioritise cases) and other clinical and social considerations. Complex cases are discussed directly with the regional ODN MDM. The numbers of patients that can be treated each month are limited by the NHSE "run rate". The regimens used to treat HCV are dictated by NHSE, with the cheapest effective NICE approved regime being recommended, With the exception of HCV genotype 2, all first line regimens are now Peg interferon (IFN) free known as direct acting antiviral (DAA) therapy, although RBV is still used in selected cases with SVR rates of > 95% irrespective of genotype, fibrosis stage or co-infection with HIV. Comparators for new HCV treatments should be with NHSE approved HCV first line regimens, with treatment populations stratified according to genotype, treatment experience (DAA exposure), presence of cirrhosis, co-infection with HIV.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The American Association for the study of Liver disease (AASLD) and European Association for Study of the Liver (EASL) publish annual updated evidence based guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Care pathways are well defined. In general there is little difference of opinion from professionals regarding treat regimens usually based on AASLD[1] or EASL guidelines[2]

• What impact would the technology have on the current pathway of care?	Provide additional treatment options for HCV therapy with regard to: 1) Re-treatment of HCV Genotypes 1 & 4 DAA exposed patients 2) Re-treatment of HCV Genotypes 3 previously exposed to (PEG)/(RBV) +/- Sofosbuvir 3) Pangenotypic treatment of HCV patients with eGFR < 30 mls/min 4) Shorter 8 week DAA regimens for most patients with HCV (Exceptions being previous DDA exposure treatment failures & HCV G3 treatment failures & those with cirrhosis) 5) RBV free & pangenotypic treatment
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	None
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary & secondary care equally applicable although decision to treat should come from secondary care.
• What investment is needed to introduce the	No additional expenditure as infrastructure as outlined in section 9 in place.

technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	In specific treatment groups – yes 1) Re-treatment of HCV G1&4 with previous DAA (particularly NS5A inhibitor) exposure [3] 2) HCV patients with renal failure (particularly HCV G2, 3 5 & 6 who have no treatment option) 3) HCV G3 treatment failures with Peg interferon & RBV ±sofosbuvir regimens & no DAA exposure
• Do you expect the technology to increase health-related quality of life more than current care?	Only in the above groups

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Greater efficacy in HCV Patients with renal failure & those HCV patients that require re-treatment as outlined above (HCV G1 & 4 DAA exposed) & HCV G3 with no NS5A exposure Contra- indicated in patients with decompensated cirrhosis (Child Pugh B &C) as increased mortality risk
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Reduction in side effects from treatment as therapy will be free from ribavirin (RBV) use. Also shorter treatment duration of 8 weeks in the majority of HCV patients will minimise exposure to side effects [4]
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	

• Is the technology a 'step-wise change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Serious adverse events have been rare in trials (<1%) [4]. Limitations of prescription are well recognised with frequent drug- drug interactions resulting in either a change in concomitant medication or the technology being contraindicated. Patients with decompensated cirrhosis are not suitable for this HCV regimen due to the risk of further hepatic decompensation and death.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Sustained virological response @ 12 weeks (SVR 12) – measured in trials
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	SVR is associated with improved long-term outcome in HCV patients [5]
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Unknown as yet
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 'Sofosbuvir–velpatasvir for treating chronic hepatitis C' [TA430]?	Yes : Sofosbuvir – velpatasvir- voxilaprevir retreatment data from Polaris (1&4) studies. These data have particular relevance regarding pangenotypic HCV treatment failure with prior DAA exposure (Polaris 1). The data from Polaris 1 & 4 studies suggest effective overall 97% SVR rates after 12 weeks of treatment. [7]
21. How do data on real-world experience compare with the trial data?	Unknown as yet as not funded by NHSE or NICE approved thus not in use outside of trials. Early access scheme commenced for patients with cirrhosis and previous treatment failure and/or renal failure in May 2017 [8] dependent on genotype.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	Not applicable

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Re-treatment of HCV G1&4 treatment failures with previous DAA (particularly NS5A inhibitor) exposure
- HCV patients with renal failure (particularly HCV G2, 3, 5 & 6 who have no treatment option)
- HCV G3 treatment failures with Peg interferon & RBV ±sofosbuvir regimens & no DAA exposure
- Shorter 8 week DAA for most patients with HCV
- RBV free pangenotypic HCV therapy

References

1) http://www.hcvguidelines.org/
2) http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/easl-recommendations-on-treatment-of-hepatitis-c-2016
3) Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. Poordad F, Felizarta F, Asatryan A et al. Hepatology. 2017 Jan 27. doi: 10.1002/hep.29081. [Epub ahead of print]
4) Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis.
5) J Hepatol. 2017 Apr 13. pii: S0168-8278(17)30211-8. doi: 10.1016/j.jhep.2017.03.039. [Epub ahead of print]

6) Simmons B, Saleem J, Heath K et al. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response Clin Infect Dis. 2015 Sep 1; 61(5): 730–740. Published online 2015 May 17. doi: 10.1093/cid/civ39

7) Bourlière, M, Gordon, SC, M.D., Flamm, SL et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. N Engl J Med 2017; 376:2134-2146 DOI: 10.1056/NEJMoa1613512

8) https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-glecaprevirpibrentasvir-for-the-treatment-of-chronic-hepatitis-c-hcv-infection-in-adult

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Glecaprevir with pibrentasvir for treating chronic hepatitis C [ID1085]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Royal College of Pathologists**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Virological cure, with reduction in the risk of long-term disease progression

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The sustained virological clearance at 12 weeks post end of therapy (SVR12) is generally considered to be the gold standard assessment of treatment response. Measures of reduction in risk of disease progression would include numbers of patients developing, and time to development of cirrhosis, decompensated complications of cirrhosis, hepatocellular carcinoma or requiring liver transplantation.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Existing NICE approved therapies have very high SVR12 rates, but there are still subpopulations of patients who would benefit from even better drug regimens e.g. those with genotype 3 infection, particularly if cirrhotic, and those who have failed interferon-based or direct acting antiviral agent-based therapy.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Through a variety of regimens of directly acting antiviral agents, the precise regimen being dependent on genotype, cirrhosis status, previous treatment experience, and cost. In practice, NICE guidelines are very much secondary to dictats by NHS England which stipulate precisely which regimen is to be used for each patient if the hospital managing that patient wishes to be reimbursed for the cost of the drugs.
• Are any clinical guidelines used in the treatment of the	NHS England issue a rate card at roughly 6 monthly intervals which specifies precisely which drugs many be used for which patients. I hesitate to call this a clinical guideline. There are guidelines available from

condition, and if so, which?	learned societies such as the European Society for the Study of the Liver and the American Association for the Study of Liver Disease.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	NHS England have set up an operational delivery network through which patients can access DAA therapy. Differences of opinion amongst professionals are irrelevant in this context as NHS England clearly stipulates which drug regimens may be used on patients.
• What impact would the technology have on the current pathway of care?	This would be entirely dependent on whether or not NHS England were prepared to allow prescription of these drugs once they are licensed. There is no doubt these drugs would be of benefit to patients who have previously failed DAA therapy, but NHS England does not currently permit use of DAAs for this purpose.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	See answers to above questions
• How does healthcare resource use differ between the technology and current care?	It wouldn't. Current care already involves the use of similar DAA drugs.
• In what clinical setting should the technology be	Currently, treatment of HCV infection has to be administered through the Operational Delivery Network set up by NHS England. This, however, is not ideal for many of the patient sub-groups who suffer from chronic

used? (For example, primary or secondary care, specialist clinics.)	HCV infection eg prisoners and people who inject drugs. Delivery of healthcare in the community would be a much better model and we should be moving towards this.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None, other than permission from NHS England to prescribe the drugs.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I would expect SVR12 rates for genotype 3 patients with cirrhosis to be improved, and likewise for certain subgroups of patients who have failed previous DAA-based therapy eg Gt1 patients who have failed previous NS5a containing regimens.
• Do you expect the technology to increase length of life more than current care?	For those patients who have failed previus DAA containing regimens, these more potent drugs offer a better chance of HCV cure
• Do you expect the technology to increase health-related quality of life more than current care?	No. An SVR12 is an SVR12, no matter which drugs induced it.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Certain subgroups of patients who have failed DAA-containing regimens. Genotype 3 cirrhotic patients
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No difference

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes – see above comments on limitation of use of all DAA drugs by NHS England
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The trial data that I have seen suggests these are more potent agents with possibly a higher barrier to resistance than some of the current DAA drugs.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No. Introduction of DAA therapy was a step-change. Introduction of second generation DAA drugs will improve SVR12 rates from very high to extremely high.
• Does the use of the technology address any particular unmet need of the patient population?	Yes for those patients who have failed NS5a containing regimens
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not aware of any significant side effect profile. Would be surprised if there was one.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Inasmuch as we would like to treat our HCV patients with all oral interferon and ribavirin free highly potent regimens with no side effects.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	SVR12 rates. Yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	SVR12 is itself a surrogate outcome. Trials to assess change in long-term outcomes are very difficult to conduct in a disease which has a natural history measured in decades, but yes, long-term morbidity and mortality data would undoubtedly be helpful.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator	Gilead are generating data using Sof-Vel-Vox

treatment(s) since the publication of NICE technology appraisal guidance 'Sofosbuvir–velpatasvir for treating chronic hepatitis C' [TA430]?	
21. How do data on real-world experience compare with the trial data?	Real world usage of DAAs results in very comparable SVR12 rates to those generated in clinical trials (I have been involved in the data collection process to prove that through HCV Research UK).
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • Access to more potent, more pangenotypic DAA drugs will increase virological cure rates • Usage of these drugs within the NHS will be entirely dependent on permission granted by NHS England • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Glecaprevir with pibrentasvir for treating chronic hepatitis C [ID1085]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UK Clinical Pharmacy Association (UKCPA) Gastroenterology and Hepatology Group**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKCPA (UK Clinical Pharmacy Association) promotes expert practice in medicines management for the benefit of patients, the public and members by establishing standards, workforce development and advancing innovation in all health care settings. The UKCPA encourages excellence, leadership and partnership.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Cure HCV

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	HCV RNA not detectable.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – HCV treatment in those with CKD where current treatment regimens are contraindicated and provides a retreatment options.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently via operational delivery networks and treatment options guided by NHSE.
• Are any clinical guidelines used in the treatment of the	Several NICE guidelines for individual drugs and choice is guided by NHSE's rate card for the time period stated.

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined – delivered via ODN pathway.
• What impact would the technology have on the current pathway of care?	Would not significantly impact the pathway of care. Would be an addition to existing options for the treatment of hepatitis C.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	No difference.
• In what clinical setting should the technology be	Secondary care, but ideally should be moving to treat patient in primary care. As a pangenotypic agent, this would be a good agent to use in hard to reach patients.

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes in patients with no current retreatment options and those with CKD and on dialysis.
• Do you expect the technology to increase length of life more than current care?	In theory if HCV is cured then could prevent progression to liver cirrhosis or even reduce cirrhosis.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No difference compared to current care.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Guided by response in viral loads.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Benefits would be in stopping the progression of fibrosis/cirrhosis. Prevention of decompensation in cirrhotic patients would be of great benefit in quality of life.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes as a retreatment option and for patients on dialysis.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes as a retreatment option and for patients on dialysis.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Nil significant adverse effects.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Sustained viral response.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Early access scheme (EAS) in place – to review adverse events if any.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance 'Sofosbuvir–velpatasvir for treating chronic hepatitis C' [TA430]?	
21. How do data on real-world experience compare with the trial data?	To review data from EAS.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • Provides a retreatment option • Provides efficacious treatment for HCV in patient with renal dysfunction • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Glecaprevir with pibrentasvir for treating chronic hepatitis C

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**On behalf of NHS England**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☒ an expert in treating the condition for which NICE is considering this technology? ☒ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England is the responsible commissioner for all hepatitis C treatments. Graham Foster is clinical lead for the HCV Operational Delivery Networks and a consultant hepatologist at Barts Health
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	[redacted] - none [redacted] - my department has received funding from AbbVie for participation in clinical trials and I have received personal fees for speaking and attending advisory boards.
Current treatment of the condition in the NHS	
6. Are any clinical guidelines	There are national guidelines for managing chronic HCV infection developed by the clinical community and a well established prioritisation process managed through regional operational delivery networks with

used in the treatment of the condition, and if so, which?	oversight from NHS England.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is very well defined and equity of access is monitored by NHS England. Resources to deliver the pathway are provided through CQUIN funding
8. What impact would the technology have on the current pathway of care?	The technology provides a welcome alternative to current technologies. All of the available technologies have excellent response rates (as evidenced by high rates of viral clearance). However for some conditions (e.g. renal impairment in patients with Genotype 3 HCV) there is no available therapy and for many conditions (e.g. Genotype 3) there is a monopoly position which reduces patient/clinician choice and reduces discounts offered to the NHS. The availability of a short duration therapy (8 weeks) for all patients with mild disease provides an opportunity for 'immediate access' to therapy without the need for viral genotyping and this may facilitate access to care for patients who have problems engaging in traditional care pathways.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health	The treatment is currently available under an Early Access to Medicines Scheme to a restricted number of patients. It is not currently available for all patients that the MA is anticipated to cover.

economy?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – NHS England anticipates that this new technology will be administered to patients according to local priorities
• How does healthcare resource use differ between the technology and current care?	Current care requires viral genotyping, disease staging and treatment in line with current NICE guidance. The new technology provides alternatives to current treatments, which may lead to increased discounts, and offers new treatment options for some subsets of patients (e.g. those with Genotype 3 infection and renal failure) as well as providing the opportunity for shorter treatment durations which may be advantageous in selected patient groups.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be delivered by Operational Delivery Networks who oversee and guide on drug selection and supervise therapy in the most appropriate clinical setting.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	NHS England fund hepatitis C treatments via a managed access programme which will fund a target of 12,500 patients in 2017/2018 – it is not envisaged that extra resource will be required for this technology appraisal.
• If there are any rules (informal or formal) for starting and stopping	Current rules recommend stopping therapy if there is evidence of virological failure and we would recommend that these rules be applied to the new technology

treatment with the technology, does this include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	None yet available
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Genotype 3 HCV is common in immigrant communities from the Indian sub-continent. Such patients currently have access to only one treatment regimen (12 weeks of sofosbuvir/velpatasvir) and this is not available to those with renal impairment as there are safety concerns in renal impairment with this existing technology. The new technology provides alternatives for this population improving their access to care.
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Addendum to NICE response (applies to all DAA treatment HTAs)
As requested, NHS England is providing an addendum to our organisation submission for ID1085 "Glecaprevir with Pibretasvir for treating chronic hepatitis C" and subsequent DAA HTAs. You have requested additional information focusing on the continuing added value to the NHS of paragraph 1.2 being included in the wording of this Technical Appraisal, consistent wi.th NICE statements governing the other treatment options for patients for this disease

> "*It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need*"

It has been indicated that the committee could be minded to conclude that continued inclusion of the statement would not add value to the guidance, informed by a number of considerations:

1. How NHS England's lack of detailed commentary reaffirming support for this aspect of NICE's current guidance was interpreted by the committee.

2. The suggestion that the use of 'multidisciplinary teams to prioritise treatment for people with the highest unmet clinical need' is no longer considered the efficient way of handling treatment decisions, and is now a straightforward tick-box exercise

3. That ODNs are an accepted route to commissioning

4. Views expressed that the capacity issues prevalent at the time of first introduction of these new drugs are no longer an issue

5. That prioritising people with highest unmet clinical needs is no longer necessary

Firstly, we set out further information that the committee will need to conclude its deliberations on the issue of ODN MDT prioritisation and treatment decisions. In our view, this information demonstrates the considerable value of the existing NICE recommendations for ODN MDTs to prioritise treatment for people with the highest unmet clinical need and thus the need for its continuation.
Secondly we set out major challenges that a fundamental change in approach caused by this proposed change at this time would create. The conditions may be right to consider such a change at some point within the coming years, but they are not appropriate today. To make revisions at a later point would avoid the disruption that will result from a change now, and avoid setting back the strategy for combating the disease to the detriment of the interests of patients and taxpayers.
As an annex to this addendum we lay out a response to each of the five considerations you have outlined to assist the committee in reconsidering this issue.

The continuing important role of ODN Multidisciplinary Teams in prioritising treatment for people with highest unmet need

The selection, commissioning, development and funding of ODNs has been a major undertaking. The value they add is to ensure that historical inequities in treatment are addressed. This planned system of care is organised to ensure the right patient gets the right treatment at the right time. Initially, ODNs have been focused on ensuring their available capacity has been used for treating those with the highest unmet clinical need – often the most severe disease. This strategy is having an impact on HCV related mortality, morbidity and demand for HCV related transplantation. NHS England considers that the ODNs have and will continue to make an important contribution. It is hard to see how the important progress made on outcomes as well as use of NHS resources - including moving from [redacted] to nearly [redacted] patients getting the lowest acquisition cost treatment option that is clinically appropriate to their treatment history, genotype, and condition - would have occurred without their important role. It is also hard to see how this would be sustained if ODNs role in prioritisation and treatment selection does not continue.
It is the clinically driven treatment choice alongside the prioritisation of patients by MDTs that has enabled the NHS to ramp up treatment choices cost-effectively. This is a clear example of the 'value-

add' from the existing guidance and the value that would be destroyed by disrupting these arrangements through removing the guidance.

The disruption of a change to the current approach at this time would set back the strategy for combatting the disease by undermining its foundation

[redacted] investment has been made by the NHS to establish and develop ODNs whose expertise and effectiveness in driving change with network partners is growing. [redacted] The ODNs are formally contracted until March 2019, [redacted] and a fundamental operational redesign of the co-ordination and organisation of treatment decisions which would deflect focus from the important role of ramping up treatment volumes and capturing vital intelligence in the new national registry and treatment outcome database.

We recognise the valuable role NICE has played in ensuring that all new DAAs are available. The guidance has underpinned NHS England's commercial activity which has used competition in the market and the principle of lowest acquisition cost for these range of effective treatments to secure an even better deal for the taxpayer. [redacted] the commercial strategy which has shown proven effectiveness based on the current guidance and has allowed reinvestment into expansion in treatment numbers to meet the projected growth forecast by NICE in previous TAs for DAAs. Removal of this element of the guidance and the commercial environment it has created would seriously affect the timing and effect of a strategic procurement we have been working on with industry involvement for over 12 months. That procurement, [redacted], aims to make elimination a reality (and possibly sooner than 2030) [redacted]

When the committee previously considered issues relating to NHS England's responsibilities it noted:

> *The responsibility for securing care for the NHS in England rests with NHS England. NICE should be cautious and sure of its judgement before requiring NHS England to provide services that it does not consider that it can provide, or provide safely and efficiently. In effect, NICE would have to conclude that NHS England was mistaken….. Its position, in setting out what it believes it needs to do to put the necessary arrangements in place, has credibility. NICE needs to be wary of substituting its judgement for NHS England's in this respect.* [1]

We would hope the committee will recognise that NHS England's responsibilities in securing care efficiently extend to applying specialist commercial expertise for bringing down prices to levels being achieved in other developed health systems, which despite some good progress to date is still yet to be achieved until our commercial strategy is fully implemented during 2018.

The National Clinical Advisory Group for Hepatitis C, who provide independent expert clinical advice NHS England have also written to NICE and to NHS England to set out their assessment of the balance of benefit and risk in making changes to this guidance. NICE has advised that for procedural reasons the committee cannot recognise that expert group as a separate stakeholder, but we feel they make an important contribution so have included their letter as annex 2 below. Their assessment aligns with our own, that continued inclusion of para 1.2 is important at the present time.

[1] TA330 Paragraph 5.8

Annex 1

1. Did NHS England's lack of detailed commentary about this aspect of NICE's current guidance suggest its declining importance?

NHS England did not include specific commentary on this point in its original submission because prioritisation of highest unmet clinical need is a fundamental principle underpinning all the NICE guidance on DAAs and in turn NHS England's sustainable roll out strategy, having been reflected in all previous TAs for DAAs. NHS England has adopted NICE's guidance on this matter and is committed to making it work.

NHS England assumed that this would continue to apply to new treatments, as has been the case in other DAA TAs. Had NHS England's position changed in relation to the importance or effectiveness of this aspect of guidance, or had there been evidence the capacity constraints giving rise to the original guidance were no longer significant, our submission would have made this point. On the contrary, it is precisely because the current arrangements **are** enabling effective ramp up in treatment levels **and** highly effective impacts on health outcomes, that NHS England believes no changes are needed to current arrangements including prioritisation at this time.

2. Is MDT decision making efficient and important or simply a tick-box exercise?

MDTs are a central feature of models of care which aim to balance access to expert advice and increasing access to treatment for patient benefit. HCV ODNs are an excellent example of this. ODN MDTs ensure through support in patient selection, treatment selection, patient support and management of complications that even local non specialist services can offer treatment to patients.
The national clinical lead for Hepatitis C and vice chair of the clinical hepatitis advisory group, Professor Graham Foster comments:

> *"Despite recent advances, treatment for hepatitis C remains complex with many patients (e.g. those with HIV infection, those with mental health problems requiring anti-psychotic agents) taking medication that can interact with the antiviral drugs. Such patients require specialist pharmacy input and support. Resistance motifs (e.g. the NS5A Y93 polymorphism in Genotype 1a that modifies response to Grazoprevir) and viral hybrids (e.g. the 'St Petersburg' 1a/2k hybrid) as well as exotic strains with novel resistance profiles (e.g. G1l) require specialist virological expertise to allow the most appropriate treatment choice. Given the cost and complexity of managing patients who have failed to respond to first line treatment it is essential that the most effective drugs are selected for initial therapy. The increasing diversity of patients with HCV who are being treated necessitates a collective approach to management – deciding when a chaotic, homeless hepatitis C infected active drug user should be considered for therapy and what support needs to be provided is not trivial and without a multidisciplinary approach such people are unlikely to be provided with the care that they need – inexperienced providers often decline to treat patients with complex co-morbidities and the MDT environment ensures equal access for all patients as well as providing education for those who are unfamiliar with these challenging individuals. ODN MDTs ensure through support in patient selection, treatment selection, patient support and management of complications that even local non specialist services can offer treatment to patients. For example in East London addiction nurse specialists now manage chaotic drug users in the community without the need for direct medical supervision – support through the MDT with shared decision making and robust assessment of the risk-benefits for each patient ensures the safety governance of this approach and provides appropriate clinical governance allowing treatment of some of the most disadvantage members of society. ODNs have ensured that the work of all local partners meet local needs for example Bart's Health ODN is working across the partner organisations to identify and prioritise treatment of patients from immigrant populations which are a high need local population whereas Brighton has chosen to focus on the needs of the homeless."*

This is far from a 'tick box exercise', as was suggested to the committee. Furthermore, far from declining, the utility of this MDT approach will be increased in the coming years as ODNs turn their attention to prioritising treatment of patients such as PWIDs which will require greater involvement of non NHS local services and models of care which effectively support adherence. In the absence of an MDT it is difficult to see how equitable access to the most effective therapies can be maintained.

3. Do capacity issues remain a relevant factor in treating Hepatitis C in 2017?

The guidance that ODN MDTs prioritise patients with the highest unmet clinical need was issued to the NHS in November 2015 and implemented in February 2016. The record of the committee deliberations state:

> *The Committee understood that NHS England considered these new oral treatments to be excellent options, but was concerned about the increase in investment and capacity needed for their implementation.*
> *The Committee heard from the patient expert that people with chronic hepatitis C appreciated the capacity constraints placed on the NHS in delivering treatment for every eligible person.*
> *The Committee recalled that treatment decisions are influenced by clinical characteristics including HCV genotype, level of liver damage, comorbidities and treatment history (see section 4.2).With these factors in mind, people with chronic hepatitis C may accept treatment being prioritised for those with highest unmet clinical need (including some people without cirrhosis), potentially determined by multidisciplinary teams.*

The backdrop to these considerations is that the NHS was on course to treat around 6,000 patients by March 2016, but Public Health England estimated there were 160,000 estimated patients with hepatitis in 2015 with around 50% thought to be diagnosed and around 4,000 new chronic diagnoses per year adding to the numbers to be treated.

It is encouraging that the NICE committee has recognised the substantial investment and attention given to developing the NHS services in the 19 months since the original guidance was implemented. The NHS is now on track to treat around 12,500 in the year to March 2018, but there remain an estimated 140,000 HCV infected patients still to treat, together with retreatment of those who fail DAAs, and new infections.

The opinion the committee heard suggesting capacity is not an issue is not borne out by the current data held by NHS England, including working hard with services in formerly underserved areas who are finding the rate of expansion NHS England is driving to be challenging.

This is not to say, the capacity picture is entirely uniformly distributed, and where clinics are struggling to achieve expansion goals, NHS England has called for clinics in other areas with localised spare clinic capacity to take on additional patient volumes, ensuring the national expansion can be achieved without sacrificing the important health equity commitment of expanding underserved areas. It is important to note there were fewer networks able to take on additional patient volumes than networks struggling with their numbers in our most recent assessment two months ago.

As increased case-finding and testing is undertaken and as treatment includes those being retreated, capacity constraints will remain and in order that ODNs can focus their attention of those with the greatest unmet need, prioritisation will continue to be required.

Our experience in working with all 22 ODNs across the country, together with the national data informs our evidence to the committee that the imbalance between demand and capacity remains substantial; hence the need for NHS England to exercise our statutory responsibility to plan capacity of the NHS to treat HCV remains. There is no consensus in the NHS that capacity issues previously considered by the committee are behind us.

4. **Is the established nature of ODNs grounds for removing recommendations about their role in prioritising and guiding treatment?**

The role, scope and authority of ODNs is inextricably linked to the existing NICE guidance, NHS England has invested in their role, not only in respect of prioritisation and prescribing decisions It is precisely because the guidance enables their role that removing the guidance would have an adverse impact on their authority to ensure treatment remains appropriate. It might be argued that the guidance still retain the requirement for ODN oversight but without prioritisation. However, the potential loss of authority of ODNs that would result from removal of their role in prioritising and guiding treatment choices is in our judgment fundamental. Furthermore, it would also adversely impact the important structures of consistent monitoring and data collection which remain vital to tracking of patients and eliminating the disease in the face of major uncertainty in expert estimates about the number of undiagnosed patients. Prioritising treatment allows oversight not only of treatment but adherence to the data quality and completeness that is critical.

5. Is it still necessary to prioritise people according to unmet clinical need?

Nationally recognised expert clinical opinion on the value of MDT consideration of treatment decisions set out above makes a strong case for the value added by MDTs in their current oversight and prioritisation role in its own right. That prioritisation is integral to this role is the inescapable conclusion of two factors: First, that demand is substantially in excess of the capacity of the NHS to treat all diagnosed patients. Second, that treating those whose health consequences are most likely to escalate ahead of those for whom such escalation is less imminent, will achieve greater health benefit if the NHS does not have the capacity to treat all patients in a short time period.

ODNs have developed approaches to prioritisation to meet the needs of their local populations. Even now, to identify just one of the risk factors for escalation that NICE previously considered, around 20% of patients being treated have cirrhosis. With the estimated 140,000 HCV infected patients still to treat, together with retreatment of those who fail DAAs and this means that there remains a real and significant potential for services to be overwhelmed by demand, and unless all patients can be treated in a short time period a sequential treatment of patients would mean more patients suffer adverse health consequences than a clinically prioritised treatment approach.

This need for prioritisation is underlined by the apparent positive progress being made on case finding. [redacted] If this serves as a proxy for diagnosis and case finding, at a rate just above the expanded rates of treatment being delivered, it supports the view that the nature of the imbalance between diagnosed patients known to services and capacity will not diminish in the near future.

To summarise our evidence in relation to the five considerations set out:

- The lack of detailed commentary previously was a sign that we believe the current guidance needs no change
- MDT decision making adds great clinical value including playing an important role in health inequalities for vulnerable individuals and is far from a tick box exercise
- Capacity issues remain a relevant factor for HCV treatment in 2017: The imbalance between demand and NHS capacity is evidenced by the national data to remain substantial
- The established nature of ODNs does not in any way remove the need to remain explicit about their role in prioritising and guiding treatment
- The greater health outcomes gain for patients from prioritised rather than sequential treatment remains as true today as it was when committee considered it 19 months ago

Having seen, as a result of the prioritisation that NICE recommended, a 10% fall in HCV mortality, and from our commissioner data an over 50% fall in HCV related transplant requirements we are keen to continue to make health gains from this approach and in the face of strong clinical evidence of benefit from the current clinical treatment strategy, a change to this approach should not be made by changing the guidance.

Annex 2

Dear Mr Boysen

I am writing on behalf of the clinical members of the NHS England Hepatitis C Advisory Group. The Advisory Group works to maximise equitable access to new HCV treatments.

At our meeting on 7th November, we received feedback on the discussion that took place at the committee meeting with regard to ID1085 "Glecaprevir with Pibrentasvir for treating chronic hepatitis C". It was noted that following discussion at the meeting NICE indicated they were minded not to include in the guidance the role of ODN MDTs, and to retrospectively remove this requirement from all published guidance. NHS England also confirmed that they had been invited to submit an addendum to their original evidence submission on this point.

We are aware that the guidance relating to the MDT and prioritisation has caused debate. Although the patient representative on the Advisory Group, Charles Gore from the Hepatitis C Trust, expressed his opposition to the principle of prioritisation, the clinical members of group are clear that the guidance, and the ODNs that implement it, play an important role with regard to the principles of:

- Securing equitable access for all patients
- Working towards the WHO goal of elimination of HCV as a public health threat by 2030

The network/MDT model of delivery was a key element of the Service Specification written by the Advisory Group in 2014, and it remains fundamental to the maintenance of universal high standards in the management of HCV.

The clinical members of the Hep C Advisory Group therefore concluded:

1. NICE appraisal of new HCV medicines is an important principle which underpins equitable access to clinically- and cost-effective medicines.

2. The guidance requirement 1.2 which states: "the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need" serves as an important cornerstone of England's strategy for sustainable roll out of HCV treatment.

3. The strategy for treatment has already resulted in significant improvements in uptake and outcomes, and the trajectory for this to continue is already set.

4. Any change in this guidance could in our opinion serve to undermine equitable access and hamper and delay efforts to eliminate the disease. We cannot see how this change would benefit patients.
The clinical members would advise that no change to guidance paragraph 1.2 is made at this time.

Yours sincerely

Peter Moss, Consultant in Infectious Diseases
Chair, NHS England Hepatitis C Advisory Group

on behalf of
Professor G R Foster
Dr K Agarwa
Professor D Mutimer

NICE National Institute for Health and Care Excellence

Clinical expert statement

Glecaprevir with pibrentasvir for treating chronic hepatitis C [ID1085]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Geoffrey Dusheiko**
2. Name of organisation	**University College London Medical School, Kings College Hospital and Skipton Fund**

3. Job title or position	**Emeritus Professor of Medicine and Consultant Hepatologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The primary aim of treatment of hepatitis C with direct acting antiviral regimens is to cure the disease. Cure is defined as a "sustained virological response" (SVR) i.e. undetectable hepatitis C virus RNA in blood by sensitive polymerase chain reaction. An SVR has been shown to reduce the progression of the disease by eliminating active hepatitis C infection and the inflammatory response to persistent hepatitis C virus infection.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Achieving SVR, halts or considerably slows the progression of liver disease. Terminating active infection also alters the likelihood of a number of HCV-induced extrahepatic morbidities, such as diabetes and renal insufficiency. An SVR is associated with normalization of serum aminotransferases and improvement or disappearance of liver necroinflammation and fibrosis in patients without cirrhosis. Hepatic fibrosis generally regresses and the risk of complications such as hepatic failure and portal hypertension is reduced in patients with severe liver disease. Recent data showed that the risk of HCC and all-cause mortality is significantly reduced (although not eliminated to zero) in patients with cirrhosis who clear HCV compared to untreated patients and non-sustained virological responders.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a continuing need for pan-genotypic and potent direct acting antivirals agent to treat patients with hepatitis C. Regimens without sofosbuvir are required for patients with severe renal impairment (stage 5 renal failure, or patients on dialysis). The advent of new regimens has driven down the cost of treatment. There is a need for new regimens to treat unsuccessfully treated patients who have developed resistance.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Hepatitis C is currently being treated with directing acting antiviral regimens that have received marketing authorisation. These regimens include sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, grazoprevir and elbasvir or paritoprevir/r, ombitasvir and dasabuvir. Treatment has been in part determined by acquisition costs.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes; NHS England has issued guidelines as has for example the European Association for the study of the Liver
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathways of care have been relatively well defined based on an extensive body of evidence derived from clinical trials and the guidelines that have been derived from the evidence. There are some gaps in the evidence around nuances such as the optimal duration of treatment or the necessity for ribavirin in sub groups of patients.
• What impact would the technology have on the current pathway of care?	Glecaprevir and pibrentasvir will prove to be an important pan-genotypic antiviral regimen. The published EC50 concentrations suggest that both glecaprevir and pibrentasvir have strong pan-genotypic potency.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Glecaprevir and pibrentasvir are listed as an option on the NHS England rate card for some categories of patients, based on least acquisition costs.

• How does healthcare resource use differ between the technology and current care?	The simplification and shortening of antiviral regimens such as the glecaprevir and pibrentasvir, often without ribavirin has reduced the need for complex monitoring during and after treatment and thus reduced resource use.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The regimen should be available to both specialists in tertiary centres as well as willing treaters, i.e.non-specialist treaters (including psychiatrists, addiction specialists, prison health care officers, clinical nurse specialists and general practitioners who have received appropriate instruction) given the overall clinical efficacy, safety and simplicity of the regimen.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No further investment other than the existing operational delivery networks for hepatitis C treatment is required. The operational delivery networks in England should assume responsibility for the instruction and training of non-specialist treaters such as those listed above to expand the number of diagnosed and treated patients.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The regimen expands options for treatment and simplifies treatment for example by reducing the need for ritonavir based regimens currently in use. The addition of this regimen has introduced competition into the market place.
• Do you expect the technology to increase length of life more than current care?	The high efficacy of regimen improves on SVR rates compared to older regimens. Currently the efficacy of direct acting antiviral treatments has been based on the primary endpoint of an SVR. The complications of chronic hepatitis C take years to occur, depending on the stage of liver disease, and clinical trials with new DAAs with SVR as main endpoint have been completed in few weeks. Thus the benefits in terms of clinical outcomes of achieving an SVR cannot be measured in these trials.

• Do you expect the technology to increase health-related quality of life more than current care?	The high SVR rates achieved with low toxicity, shorter duration in some patients without ribavirin in many cases would be expected to at least match the widely reported HRQOL for other regimens. However, this reviewer has not seen a detailed HRQOL analysis for glecaprevir plus pibrentasvir at the time of writing this report. In general however an patient reported outcomes of health quality have been an encouraging aspect of an SVR
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The regimen would be broadly effective for a wide array of patients with genotype1-6 and compensated cirrhosis. Patients with advanced renal disease would benefit from the absence of sofosbuvir, for which dosing information is yet lacking. The regimen may be used in liver transplant recipients, although the evidence has not been gathered in this population. The regimen could be used in HIV coinfected patients. Most patients would manage to take the three 100 mg/40mg tablets once daily. The regimen would be suitable for re-treatment of patients who have been unsuccessfully treated with pegylated interferon and ribavirin with or without sofosbuvir or those unsuccessfully treated with sofosbuvir and ribavirin, with or without cirrhosis Patients with decompensated cirrhosis (Child-Pugh B or C) would not be candidates for treatment with this regimen as the protease inhibitor (glecaprevir) would be contraindicated. 16 weeks is recommended for treatment experienced genotype 3 patients with or without cirrhosis. The safety of the regimen has not been determined in children and adolescents younger than 18 years. The use of this regiment in patients unsuccessfully treated with prior NS3A and /or NS5A inhibitors requires further evidence: Genotype 1-infected (and a very small number of genotype 4-infected) patients with prior failure on regimens that may confer resistance to glecaprevir/pibrentasvir were treated in the MAGELLAN-1 study. The risk of failure was highest for those exposed to both classes of antiviral agents. No re-treatment data is available for patients infected with genotypes 2, 3, 5 or 6. The regimen is not recommended in the SMPC for the re-treatment of patients with prior exposure to both a NS3/4A- and NS5A-inhibitors. Retreatment It could be suggested that resistance testing (by population sequencing will be required before utilising the regimen. Some substitutions at position 156 reduced susceptibility to glecaprevir (genotypes 1 to 4) by more than 100-fold. Substitutions at amino acid position 80 did not reduce susceptibility to glecaprevir except for Q80R in genotype 3a, which reduced susceptibility to glecaprevir by 21-fold.

	Single NS5A inhibitor class resistance substitutions at positions 24, 28, 30, 31, 58, 92, or 93 in NS5A in genotypes 1 to 6 had no impact on the activity of pibrentasvir. In genotype 3a, A30K or Y93H had no impact on pibrentasvir activity. Some combinations of substitutions in genotypes 1a and 3a (including A30K+Y93H in genotype 3a) showed reductions in susceptibility to pibrentasvir. From the SMPC: “Cross-resistance In vitro data indicate that the majority of the resistance-associated substitutions in NS5A at amino acid positions 24, 28, 30, 31, 58, 92, or 93 that confer resistance to ombitasvir, daclatasvir, ledipasvir, elbasvir, or velpatasvir remained susceptible to pibrentasvir. Some combinations of NS5A substitutions at these positions showed reductions in susceptibility to pibrentasvir. Glecaprevir was fully active against resistance-associated substitutions in NS5A, while pibrentasvir was fully active against resistance-associated substitutions in NS3. Both glecaprevir and pibrentasvir were fully active against substitutions associated with resistance to NS5B nucleotide and non-nucleotide inhibitors.” However further resistance testing in patients and further clinical experience is required to determine the efficacy in patients unsuccessfully treated with NS3A and NS5A inhibitors.
The use of the technologytr	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	The regimen will be relatively easy to use and no more difficult than other direct antivirals currently in use by the NHS. The 8 week regimen will favour throughput through specialist and non-specialist clinics. Drug drug interactions: from the SMPC: Concomitant use with atazanavir containing products, atorvastatin, simvastatin, dabigatran etexilate, ethinyl oestradiol-containing products, strong P-gp and CYP3A inducers (e.g., rifampicin, carbamazepine, St. John's wort (Hypericum perforatum), phenobarbital, phenytoin, and primidone) is contraindicated.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	At present the rules should follow the SMPC for the regimen. All potential drug drug interactions will require mandatory checking because of potential interactions. The important interactions are listed in the SMPC. However, the task of ruling out drug drug interactions is considerably facilitated by the Liverpool hepatitis C web site and app.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It is possible that increased case finding and widespread successful treatment of hepatitis C will reduce the prevalence and incidence of hepatitis C in the population. Studies to prove this supposition are required. Extra hepatic manifestations of hepatitis C are likely to be improved.
17. Do you consider the technology to be innovative in its potential to make a	The regimen is an important addition to current treatments for chronic hepatitis C. Competition, and lowering or prices will advance access to treatment.

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The technology introduces a potent and highly effective regimen to current treatments. Glecaprevir and pibrentasvir are large improvements over the current ritonavir based regimen of paritaprevir, ombitasvir and dasabuvir and improve the overall outlook for treatment experienced genotype 3 patients.
• Does the use of the technology address any particular unmet need of the patient population?	As noted above: treatment of genotype 3 patients with renal failure
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile of the regimen are minimal, and the regimen can be widely applied to diverse groups of patients including more vulnerable patients currently using injecting drugs, and patients with severe psychosocial morbidity. HRQOL studies show encouraging results for DAA therapies after a sustained virological response
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The outcomes measured in these trials were SVR, as noted above.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The harmful effects of chronic hepatitis C take years to develop in patients that generally remain asymptomatic for long periods of time. Recent data have suggested that the risk of disease progression and severe outcomes are reduced in patients who achieve and SVR. The recent Cochrane review failed to understand that these outcomes could not be assessed at maximum follow up short term clinical trials.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No major adverse events have come to light since the marketing authorisation was granted.
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Real world data have not been gathered. However real world data have generally emulated the clinical trial data for direct acting antivirals, largely because of the very high efficacy of current direct acting antiviral therapies for hepatitis C
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The issues related to widespread equity of access for marginalised but at risk groups with a high prevalence and incidence of hepatitis C
22b. Consider whether these issues are different from issues with current care and why.	A new strategic framework based on WHO elimination targets for hepatitis C is required rather than the current run rates and quotas for treatment. Case finding and referral for care is a priority.
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- The regimen is an important pan-genotypic regimen
- 8 weeks treatment will suffice for some groups
- The regimen will not require dose adjustment for patients with stage 5 renal failure
- The regimen is contraindicated for patients with decompensated (Childs B and C) cirrhosis
- The potency of the protease and NS5A inhibitor in the regimen could form part of retreatment regimen

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Glecaprevir-pibrentasvir for treating chronic hepatitis C

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors
Rob Riemsma, Reviews Manager, Kleijnen Systematic Reviews Ltd, UK
Isaac Corro Ramos, Health Economics Researcher, EUR, NL
Nasuh Büyükkaramikli, Health Economics Researcher, EUR, NL
Debra Fayter, Systematic Reviewer, KSR Ltd, UK
Nigel Armstrong, Health Economist, KSR Ltd, UK
Steve Ryder, Health Economist, KSR Ltd, UK
Ciara Keenan, Systematic Reviewer, KSR Ltd, UK
Stephanie Swift, Systematic Reviewer, KSR Ltd, UK
Vanesa Huertas Carrera, Systematic Reviewer, KSR Ltd, UK
Piet Portegijs, Systematic Reviewer, KSR Ltd, UK
Shelley de Kock, Information Specialist, KSR Ltd, UK
Gill Worthy, Statistician, KSR Ltd, UK
Maiwenn Al, Associate Professor of Health Economics, EUR, NL
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to Rob Riemsma, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD

Date completed 28/09/2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number STA 16/168/09.

Declared competing interests of the authors
None for the authors. Dr Ryder attended paid advisory boards for Gilead, Abbvie, and MSD. Dr Millson received sponsorship for department and meetings from Gilead, Abbvie and MSD.

Acknowledgements
We are very grateful to the following experts who offered clinical advice and comments on the draft report:

- Dr Stephen Ryder, Consultant Hepatologist at Nottingham University Hospital Trust; and
- Dr Charles Millson, Consultant Hepatologist/Gastroenterologist at York Teaching Hospitals NHS Foundation Trust.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

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.

This report should be referenced as follows:
Riemsma R, Corro Ramos, I, Büyükkaramikli N, Fayter D, Armstrong N, Ryder S, Keenan C, Swift S, Huertas Carrera V, Portegijs P, De Kock S, Worthy G, Al M, Kleijnen J. Glecaprevir-pibrentasvir for treating chronic hepatitis C; A Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2017.

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. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Isaac Corro Ramos, Nasuh Büyükkaramikli, Nigel Armstrong and Steve Ryder acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter, Ciara Keenan, Stephanie Swift, Vanesa Huertas Carrera and Piet Portegijs acted as systematic reviewers, 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. Shelley de Kock 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

AE	Adverse events
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ART	Anti-retroviral treatment
BI	Budget impact
BNF	British National Formulary
BOC	Boceprevir
BSC	Best supportive care
C	Cirrhotic
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Compensated cirrhosis
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
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Cost utility analysis
DAA	Direct-acting antivirals
DAE	Discontinuation due to adverse events
DCC	Decompensated cirrhosis
DCV	Daclatasvir
DCV/RBV/IFN	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
EBR/GZR	Elbasvir/grazoprevir
EBR/GZR + RBV	Elbasvir/grazoprevir with ribavirin
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EODBT	End of double-blinded treatment
EOT	End of treatment
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

eRVR	Extended rapid viral response
ESLD	End-stage liver disease
ESRD	End stage renal disease
EUR	Erasmus University Rotterdam
EVR	Early viral response
FAD	Final appraisal determination
FDA	Food and Drug Administration
FIB	Fibrosis
FSS	Fatigue Severity Scale
G/P	Glecaprevir in combination with pibrentasvir
GT	Genotype
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCHS	Hospital and Community Health Service
HCV	Hepatitis C virus
HCVTSat	Chronic HCV treatment satisfaction instrument
HIV/HIV-1	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HUI3	Health Utilities Index Mark 3
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
IFN	Pegylated-interferon alpha
IFN + RBV	Pegylated-interferon alpha in combination with ribavirin
ITC	Indirect treatment comparison
ITT	Intention to treat
ITT-MS	ITT mono-infected HCV GT1 population
ITT-PS	ITT mono-infected GT1 DAA-naïve
ITT-PS-PP	Per-protocol ITT-PS population
KSR	Kleijnen Systematic Reviews
LDV	Ledipasvir
LDV/SOF	Ledipasvir in combination with sofosbuvir
LDV/SOF/RBV	Ledipasvir in combination with sofosbuvir, with ribavirin
LFT	Liver function test
LLOQ	Lower limit of quantitation
LSMD	Least squares mean difference
LT	Liver transplant
LYS	Life year saved
MAIC	Matching-adjusted indirect comparison
MCMC	Markov Chain Monte Carlo
MeSH	Medical subject headings
MCS	Mental component summary
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
MRU	Medical resources utilisation
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
NMA	Network meta-analysis
NR	Not reported
NS5A	Non-structural protein 5A
OAE	Overall adverse events
OBV/PTV/RTV	Ombitasvir–paritaprevir–ritonavir
OBV/PTV/RTV + DSV	Ombitasvir–paritaprevir–ritonavir with dasabuvir
OBV/PTV/RTV + RBV	Ombitasvir–paritaprevir–ritonavir with ribavirin
OBV/PTV/RTV + DSV + RBV	Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin
OD	Once-daily
OL	Open label
ONS	Office of National Statistics
OS	Overall survival
PAS	Patient access scheme
PCR	Polymerase chain reaction
PPI	Proton pump inhibitor
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome
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
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
SE	Standard error
SF-36	Short form 36
SF-6D	Short-Form Six-Dimension
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/SOF	Simeprevir in combination with sofosbuvir
SoC	Standard of care
SOF	Sofosbuvir
SOF/RBV	Sofosbuvir in combination with ribavirin

SOF/RBV/IFN	Sofosbuvir in combination with ribavirin, with pegylated-interferon alfa
SOF/VEL	Sofosbuvir–velpatasvir
STA	Single technology appraisal
SVR	Sustained virologic response
TE	Treatment-experienced
TE-PR	TE with regimens containing peg-IFN/RBV
TE-PRS	TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN
TN	Treatment-naïve
TVR	Telaprevir
UK	United Kingdom
UMC	University Medical Centre
VAS	Visual analogue scale
WHO	World Health Organisation
WPAI-HCV	Work Productivity Activity Impairment Hepatitis C Specific Instrument
WTP	Willingness to pay

Table of Contents

Table of Tables

Table of Figures

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 glecaprevir-pibrentasvir (G/P) 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, daclatasvir (DCV) in combination with sofosbuvir (SOF) (for GT1 and GT4); pegylated-interferon alfa (IFN) with RBV and SOF in combination with RBV (for GT1 and GT4) were not included in the decision problem. The rationale for these omissions, as supplied by the company, states that these treatment regimens are not used in current NHS practice.

The company's model does not include the development of resistance to G/P and other comparators based on the assumption that this outcome does not impact the cost effectiveness of G/P. Also, separate subgroup analyses for patients who are co-infected with HIV, previous treatment received (with or without DAA-containing regimens), people who have received treatment before liver transplantation, and those who have received it after liver transplantation, response to previous treatment (non-response, partial response, relapsed), and people with and without renal impairment were not presented, as it was deemed infeasible by the company.

1.2 Summary of clinical effectiveness evidence submitted by the company

Eighty-one publications (reporting on 79 studies) were identified as meeting the eligibility criteria. Fourteen of these publications, representing seven studies, involved G/P. In addition, information on four further clinical studies of G/P in patients with CHC are mentioned in the company submission. These studies were conducted in special populations of patients with HIV co-infection, renal impairment, failure on prior DAAs and a post-transplant population. Finally, the company mentioned two trials in Japanese patients with CHC: CERTAIN-1 and CERTAIN-2. These trials are only minimally discussed in the CS and not included in the economic model. According to the company, this exclusion was because "these two trials were conducted entirely in Japanese patients" which "precludes their generalisability to the UK patient population and subsequently their use in the economic model". Apart from these two trials in Japanese patients, none of the included studies presented comparative data for the licensed treatment duration of G/P with any of the comparators.

The G/P studies included patients with all genotypes; treatment-naïve and treatment-experienced patient populations; and patients with 'no cirrhosis or compensated cirrhosis'.

When split by cirrhosis status and previous treatment (naïve or experienced), SVR rates were consistently above 90% for all genotypes, except for GT2/TE/NC ([redacted] in SURVEYOR-II, Part 4; but [redacted] in SURVEYOR-II, Parts 1 and 2), GT3/TE/CC ([redacted] in SURVEYOR-II, Part 2; but [redacted] in SURVEYOR-II, Part 3) and GT6/TN/NC ([redacted] in SURVEYOR-II, Part 4).

[redacted] In studies without a comparator, many treatment arms [redacted]

According to the company, G/P had a favourable safety profile that was similar to placebo and SOF/DCV, and that was similar across treatment durations of 8, 12, and 16 weeks. G/P was well

tolerated across a broad and diverse population of patients, including patients with CC, HIV co-infection, and CKD Stage 4/5. Common study adverse drug reactions (ADRs) occurring in ≥5% of patients were headache, fatigue, and nausea. Adverse drug reactions were mostly Grade 1 (mild) in severity. Serious ADRs and ADRs leading to premature study drug discontinuation were rare (≤0.1%).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company submission (CS) and response to clarification provided sufficient detail for the ERG to appraise the searches for eligible trials. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4 using a good range of databases. Additional searches of conference proceedings were conducted but no separate literature searches were undertaken to identify adverse events data, non-randomised and non-controlled evidence.

The conclusion from the G/P studies is that G/P has high SVR rates in all genotypes. In addition, G/P has a relative favourable safety and tolerability profile. However, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each group. Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators relies on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. In most cases the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.

1.4 Summary of cost effectiveness submitted evidence by the company

The company developed a de novo cost effectiveness model to assess the cost effectiveness of G/P compared to nine different comparators: BSC-watchful waiting, DCV/SOF, DCV/SOF/RBV, EBR/GZR, LDV/SOF, OBV/PTV/DSV+DSV ± RBV, PR, SOF/PR, SOF/RBV and SOF/VEL. The cost effectiveness analyses performed by the company are in line with previous STAs for HCV treatments. The population considered in the cost effectiveness analyses was sub-divided into 26 different subgroups, where patients were stratified by genotypes (GT1, GT2, GT3, GT4, GT5 and GT6), treatment experience (treatment-naïve and treatment-experienced patients), cirrhosis status (cirrhotic and non-cirrhotic patients) and IFN-eligibility (only for GT2 TN patients). Full incremental cost effectiveness results were presented for all subgroups. A National Health Service (NHS) and Personal and Social Services (PSS) perspective was adopted with a lifetime time horizon. A 3.5% discount rate was used for both costs and quality-adjusted life years (QALYs).

The cost effectiveness model developed for this submission was a Markov model which consists of 13 health states. Non-cirrhotic patients start from states F0-F3, and cirrhotic patients start from F4. All treatment related outcomes (achieving SVR, treatment related adverse events and discontinuation) occur within the first year of the model. Patients who do not achieve SVR are at risk of progressing to more severe states. Patients who reach F4 can progress to DC and HCC states, which may lead to liver transplantation and liver-related death. The liver transplantation state was divided into two categories (first year and later years).

Treatment effectiveness was modelled as the probability of achieving SVR. Other treatment-specific parameters included adverse event rates, treatment duration, and treatment-related utility adjustments. All these parameter estimates were based on naïve indirect comparison of clinical trials assessing the efficacy of G/P and its comparators in the relevant subgroups.

The model uses health state based utilities from the literature (utilities that were used in Wright et al. 2006 and Ratcliffe et al. 2002) in line with previous STAs for HCV treatments. A utility increment due to SVR is applied based on Shepherd et al. 2007 and Hartwell et al. 2011. Treatment-related health utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events.

List prices were used as treatment costs for G/P and the comparator treatments in the cost effectiveness analysis. Health state costs (disease management costs based on disease stage) and other costs for adverse events were based on literature, expert opinion, UK reference costs and previous appraisals for HCV (especially TA430).

The base-case cost effectiveness results showed that for non-cirrhotic patients, G/P was always cost effective except for two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).

Additionally, the company conducted probabilistic, deterministic and scenario analyses. Probabilistic results were reported as the probability that G/P is cost effective against one single comparator for each subgroup at £20,000 and £30,000 thresholds. The comparator was selected as the one against which G/P had the lowest incremental net monetary benefit when valuing a QALY at £20,000. The result of the deterministic sensitivity analyses showed that in general the ICER was most sensitive to changes in SVR rates. Two scenario analyses conducted by the company first demonstrated how the cost effectiveness of G/P might change after the CMU price agreement (when comparators from other companies were based on list prices). Second, it was shown that using trial-based utilities increased total QALY estimates compared to the base-case when literature-based utilities were used as input.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The CS and response to clarification provided sufficient detail for the ERG to appraise the cost effectiveness searches. Searches were well documented but not all searches were reproducible in line with the NICE guide to the methods of technology appraisal. However, a good range of databases were searched and additional searches of conference proceedings were also undertaken.

The following treatments were not included in the cost effectiveness analyses because, according to the company, these are not used in current NHS practice: 1) DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE); 2) IFN with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients); 3) SOF in combination with RBV, with or without IFN (for specific people with GT1 and GT4; as recommended by NICE). The IFN eligibility

was only considered for GT2, however it was not clear why there was no IFN containing regimen as a comparator for the GT2 TN CC (IFN-eligible) subgroup.

Despite being included in the final scope, the company did not perform subgroup analyses for patients who are co-infected with HIV and post-liver transplantation. The subgroup of patients who are intolerant to or ineligible for interferon treatment were only considered for GT2 TN patients. Since these excluded groups (e.g. HIV co-infected patients) were also not taken into consideration while deriving some of the model input estimates (e.g. utility), transferability of the current results for these groups is disputable. Furthermore, heterogeneity of the treatment-experienced population was not taken into account. (e.g. whether a patient is intolerant or an inadequate responder to the previous therapy, or has already received a DAA treatment or maybe is DAA naïve, may all impact the effectiveness of G/P).

Onward transmission is not included in the economic model. Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework. Similarly, the company assumed a zero-reinfection probability after reaching SVR and assumed that no natural recovery takes place, despite contrary evidence reported in the clinical literature.

SVR rates, adverse event rates, treatment duration, and treatment-related utility adjustments were based on naïve indirect comparisons of clinical trials assessing the efficacy of G/P and its comparators in the relevant subgroups. The ERG has concerns on the plausibility of this approach, which is not in line with evidence synthesis best practices and is susceptible to bias. Furthermore, some of the SVR rates were either derived from very small sample sizes or the effectiveness in a subgroup was assumed to hold in another subgroup. Since SVR rates are the main driver of costs and effectiveness, all these assumptions create a substantial uncertainty on the cost effectiveness of G/P.

Furthermore, it was not clear to the ERG why age-dependent transition probabilities were not updated every year.

The health state utilities from RCTs could have been used by the company in their cost effectiveness analysis instead of the utilities from the literature. The ERG questions to what extent utility values published in 2006 (originating from EQ-5D questionnaires completed in 2002), i.e. before the DAA-era, can be seen as representative of UK patients currently suffering with CHC. Similarly, the RCT-based utility values show a difference in utility with or without SVR ranging from 0.025 to 0.029, substantially lower than the increment of 0.05 applied by the company based on Wright et al. 2016 thus raising doubt about the validity of the latter value.

The ERG was unsure about the completeness of the health state cost estimates used in the model, as items such as GP visits and home care costs are not included.

The ERG is concerned over the validation status of the cost effectiveness analysis by the company. The tests conducted for the technical verification of the model were not presented and the only validation effort was the external validation of the model estimates of the cirrhosis risk in 20 years from the clinical literature.

Despite the several uncertainties present in the CS base-case, the ERG did not produce an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisal. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses.

There are two major flaws in the probabilistic analyses presented by the company. The first is considering a single comparator instead of all possible comparators in the analyses. The second is the failure to include a large number of SVR and AE rates (i.e. all that have a value of 100% and 0%) in the probabilistic analyses. As a consequence, the ERG considers the PSA results in the CS unreliable. Given the time constraints and the model complexity, the ERG could not produce detailed (corrected) PSA results for all subgroups, only for a few example subgroups. If it is judged that the analysis of uncertainty is a major concern for this submission, the PSA analyses should be repeated after tackling the issues discussed in this report.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The majority of searches for eligible studies in the CS were well documented. Searches were carried out in a good range of databases and strategies utilised study design filters. In response to clarification questions, a number of searches were repeated to ensure all relevant evidence had been included. Supplementary searches of conference proceedings were also undertaken.

The company's submitted evidence on clinical effectiveness broadly covered the final scope set out by NICE. The review of G/P studies included all relevant studies in which G/P 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 structure of the economic model developed by the company is in line with previous models presented in appraisals for HCV submitted to NICE. Thus, the model structure (not necessarily inputs) reflects the main aspects of the chronic HCV disease. The model also includes relevant adverse events, utilities and costs.

1.6.2 Weaknesses and areas of uncertainty

Clinical effectiveness searches were re-run in response to clarification questions but did not include a number of comparators from the original search. Conference searches also did not look for the intervention of interest in addition to some comparator interventions. Cost effectiveness searches that were re-run in response to clarification questions added a restrictive UK country filter, which may have resulted in relevant evidence being missed. There is also concern about the effectiveness of the Embase search for health-related quality of life as the company did not present the full set of records that they claimed to have screened. Some searches were also not reproducible in line with NICE guide to the methods of technology appraisal. There were no searches for adverse events data, non-randomised and non-controlled evidence.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators rely on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how responses and adverse events for comparator studies were selected and whether all possible sources were used. In most cases, the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.

In addition, patient numbers for most GT4, GT5 and GT6 populations in G/P studies are very low, often less than 10 patients in each subgroup. Only three out of the 24 subgroups included more than 100

patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

Since the key parameters in the cost effectiveness analyses (SVR rates) were based on the treatment effectiveness data, all health economic analyses suffer from the uncertainty of clinical effectiveness (i.e. comparative SVR rates). Furthermore, all analyses were conducted on list prices, which may not reflect the actual costs of the treatments to the NHS. Both probabilistic and sensitivity analyses presented by the company were performed incorrectly. As a consequence, the ERG considers the sensitivity analysis results in the CS unreliable. If it is judged that the analysis of uncertainty is a major concern for this submission, these analyses should be repeated after tackling the issues discussed in this report. The company submission would also benefit from a more transparent electronic model.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has not presented an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses. In the scenario analyses assumptions surrounding the utility gain due to SVR, impact of the treatment on utility, impact of age on utility were challenged. In addition, alternative inputs for transition probabilities between fibrosis stages and re-infection rates were explored. Even though these scenarios changed the total costs and/or total QALYs estimates, the impact on incremental results was minimal. The cost effectiveness of G/P in each subgroup did not change, hence the cost effectiveness results of the base-case seem to be robust to changes in utility and treatment-unrelated clinical model inputs.

Additionally, the exploratory PSA analyses conducted by the ERG showed that that the inclusion of parameter uncertainty around all SVR and AE rates (which was not included in the company's base-case when rates were 100% or 0%) can have a major impact on the G/P cost effectiveness probability for certain subgroups; but also that this impact can go in either direction (although more frequently it decreases the G/P cost effectiveness probability). This was especially striking for GT5 TN NC patients, for whom the company might have overestimated the probability of G/P being cost effectiveness by 66 percent. Furthermore, the ERG showed that the PSA outcomes were enormously scattered over the CE plane quadrants for a number of subgroups, which illustrates the main limitation of presenting cost effectiveness probabilities alone (as in the CS).

2. BACKGROUND

This report provides an appraisal of the evidence submitted by Abbvie in support of Glecaprevir/Pibrentasvir (G/P) (tradename: Maviret®) for the treatment of chronic hepatitis C virus (HCV) infection in both treatment-naïve (TN) and treatment-experienced (TE) populations. Maviret is a fixed dose combination of two directly-acting anti-viral agents (DAAs) that interfere with viral replication: Glecaprevir, an NS3/4a protease inhibitor, and Pibrentasvir, an NS5a inhibitor. The EMA granted G/P full market authorisation on 26 July 2017.[1] In this section, we outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken mainly from section B1.3 of the company submission (CS) and the references to support this section of the submission have also been examined.

2.1 Critique of company's description of underlying health problem

The target disease in this appraisal is chronic hepatitis C infection. The CS states that in approximately 15 to 25% of patients with acute HCV infection the disease is resolved, whilst the remaining 75 to 85% of patients progress to chronic HCV infection, defined as the presence of HCV RNA in the serum for >6 months.

The CS states that HCV prevalence levels correspond to a chronically infected worldwide population of approximately 170 million people, with 3 to 4 million new cases of HCV infection globally each year. The company adds that, in the UK, *it has been suggested that 86% of individuals infected with the virus are unaware they have been infected*,[2] which presents an issue for heightened risk of onward transmission. The CS further states that *the burden of HCV infection in England and Wales is largely carried by current and ex-PWIDs*.[2]

The CS explains that six major genotypes (GT1–6) and 67 subtypes of HCV have currently been identified. The CS describes that in England, HCV genotypes GT1 and GT3 are most prevalent, accounting for 47% and 44% of HCV infection cases, respectively, with other genotypes contributing the remaining 9%.[3]

ERG comment:

The company submission includes an appropriate description of the disease. However, several details are sparsely reported. For example, there is no discussion in the CS of the proportion of people who fail to respond to current treatments or develop treatment resistance (specifically to DAA therapies).

The ERG would like to add the following:

- Certain subgroups of patients are at a higher risk of progressing to chronic hepatitis C (CHC) i.e. African-Americans, HIV-infected individuals, men and those >25 years of age, since this provides a rationale for some of the sub-group analyses proposed in the scope of this submission.[4]
- The CS does not include prevalence data on HCV in England. Recent estimates are that approximately 160,000 people have chronic hepatitis C in England.[5]
- Aetiology and routes of infection are only briefly mentioned in the CS. Injection drug use continues to be the most important risk factor for HCV infection, as supported by approximately 90% of all reports where risk factors have been disclosed.[5]

The company discuss the risks and associated burdens of HCV. The CS states that, depending on whether co-factors are present (e.g. alcohol consumption), 10 to 20% of patients progress to cirrhosis

over 20 to 30 years. They highlight that infection with HCV GT3 is associated with the highest risk of developing cirrhosis and hepatocellular carcinoma (HCC).

The CS states that *once cirrhosis has developed, patients have a 1 - 5% annual risk of progression to decompensated cirrhosis (DCC)*.[2]

The CS adds that *CHC is also associated with several extra-hepatic manifestations, including the development of mixed cryoglobulinaemia and its sequelae (ranging from cutaneous and visceral vasculitis to glomerulonephritis and B-cell non-Hodgkin's lymphoma), as well as increased rates of insulin resistance, diabetes, and atherosclerosis, which may lead to increased cardiovascular morbidity and mortality.*[6] *Neurological manifestations of HCV infection include fatigue and cognitive impairment.*[6]

The CS explains that health-related quality of life is lower in individuals suffering from CHC compared to the general population. They further state that current treatment options may also pose a considerable burden on HRQoL for some patient subgroups. As an example they state that *treatment with peg-IFNa plus RBV is associated with a variety of toxic side-effects.*[2]

The company cite evidence that in the UK, mortality rates among HCV-infected patients have been shown to be three times higher than expected relative to the general population of England. However they state that *the introduction of new direct-acting anti-viral (DAA) drugs may be starting to have an impact on HCV-related mortality, with a fall of 8% in HCV-related ESLD and HCC deaths in 2015.*[3]

ERG comment:

The risks and burdens of HCV have been appropriately discussed. The ERG noted the following:

- The risk of progression to decompensated cirrhosis is 3 to 6% according to the reference cited in the CS.[7] The quoted 1 to 5% annual risk values pertain to the risk of progression to *hepatocellular carcinoma*.[7]
- The study of UK mortality rates among HCV-infected patients used in the CS is considered to be reliable. However, whilst this study was relatively large, it only recruited patients from the Trent region of England, and there is clear evidence that regional disparities exist in the UK in terms of HCV prevalence and HCV-associated mortality.[8]

2.2 Critique of company's overview of current service provision

The company presents a matrix of NICE-recommended therapies according to genotype, presence of cirrhosis and previous treatment. This matrix is duplicated below.

The CS states that there is *no NICE clinical guideline for hepatitis C to then distinguish which of the NICE-recommended therapies might represent standard of care.*[2]

The company claims that a number of NICE-approved therapies do not form part of clinical practice in England. This was based on expert clinical opinion and on a review of the European Association for the Study of the Liver (EASL) guidelines.[9]

- In particular, the CS highlights that the use of peginterferon and ribavirin (RBV) alone is reducing in clinical practice. This is due in part, to the adverse effects associated with interferon. They also state that *it is assumed that there will be no patients receiving peg-IFNa + RBV across any genotype and subgroup in which SOF / VEL is recommended by NICE*.[2]
- Secondly, the CS states that daclatasvir (DCV) in combination with sofosbuvir (SOF) with/without RBV is not used in clinical practice in England for patients with GT1 and GT4.

DCV in combination with SOF without RBV is only considered in the submission as a comparator to G/P for GT3 patients.

- Thirdly, the CS states that SOF in combination with RBV with / without peg-IFNa is not used in clinical practice in England for patients with GT1 and GT4. This combination is only considered a comparator to G/P in the appraisal for GT2, GT3, GT5 and GT6 patients.

The CS stresses that currently the only direct-acting antiviral (DAA) regimen suitable for all six genotypes, and without RBV and IFN, is SOF/VEL. However, they discuss some limitations with this drug: *'in GT2, SOF/VEL is only recommended for TN non-cirrhotic (NC) patients who cannot tolerate IFN-based treatments'.*[2]

The positioning of G/P is across all the genotypes of HCV. The company state that a large proportion of patients (TN NC (non-cirrhotic)) would be able to receive a short treatment (eight weeks). There would be the potential to remove the requirement to genotype any TN NC patients. This in turn would mean that the intervention could be delivered in the community which would improve access to treatment for difficult to engage populations. The company also highlights the specific populations who might benefit including those with severe renal impairment and specific TE GT 3 patients.

ERG comment:

- The complexity of the changing treatment landscape is appropriately outlined by the company.
- The reduction of peg-IFNα and RBV use in the HCV population and the adverse events associated with IFN-based regimes is appropriately outlined.
- Our clinical expert supported that the three regimes highlighted in the bullet points above are no longer relevant to clinical practice.
- Our clinician advises us that the statement '*in GT2 SOF/VEL is only recommended for TN non-cirrhotic (NC) patients who cannot tolerate IFN-based treatments'* is incorrect and that oral therapy is now recommended and funded for G2 NC patients.
- Within this report the role of G/P will be evaluated by genotype, prior treatment experience and presence of cirrhosis as presented by the company. Any changes to the clinical pathway such as removal of the need to genotype or intervention setting in relation to treatment-naïve non-cirrhotic patients would depend on approval for all genotypes.

Table 2.1: Matrix of NICE-recommended therapies for chronic hepatitis C

Geno-type	Treatment (duration in weeks)			
	TN-NC	**TN-C**	**TE-NC**	**TE-C**
1	• SOF/VEL (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (24/48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • SOF/LDV (8) • OBV/PTV/RTV + DSV (12), 1a: + RBV • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (24), or peg-IFN + RBV (4) then BOC + peg-IFN + RBV (32) then peg-IFN + RBV (12)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (12), or TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) Treatments only recommended for patients with significant fibrosis[c]: • SOF + DCV (12)	• SOF/VEL^{+} (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (24/48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • *SOF/LDV (12) • *OBV/PTV/RTV + DSV + RBV (12), 1a: (24)[b] • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) Treatments only recommended for IFN-ineligible patients: • *SOF + DCV ± RBV (24)	• SOF/VEL (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • SOF/LDV (12) • OBV/PTV/RTV + DSV (12), 1a: + RBV • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (32) then peg-IFN + RBV (12), or peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (12), or TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) Treatments only recommended for patients with significant fibrosis[c]: • SOF + DCV (12)	• SOF/VEL^{+} (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (48)* • EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV • *SOF/LDV[a] (12) • *OBV/PTV/RTV + DSV + RBV (12), 1a: (24)[b] • *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)* • *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)* • Best supportive care (watchful waiting) Treatments only recommended for IFN-ineligible patients: • *SOF + DCV ± RBV (24)
2	• Peg-IFN + RBV (24) • Best supportive care (watchful waiting)	• SOF/VEL^{+} (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL^{+} (12) • SOF + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL^{+} (12) • SOF + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)

Geno-type	Treatment (duration in weeks)			
	TN-NC	**TN-C**	**TE-NC**	**TE-C**
	Treatments only recommended for IFN-ineligible patients: • SOF/VEL (12) • SOF + RBV (12)	Treatments only recommended for IFN-ineligible patients: • SOF + RBV (12)		
3	• SOF/VEL (12) • Peg-IFN + RBV (24) • Best supportive care (watchful waiting) Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]: • SOF + DCV (12)	• SOF/VEL^{+} ± RBV (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) Treatments only recommended for IFN-ineligible patients: • SOF + RBV (24) • *SOF + DCV + RBV (24)	• SOF/VEL (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]: • SOF + DCV (12)	• SOF/VEL^{+} ± RBV (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting) Treatments only recommended for IFN-ineligible patients: • SOF + RBV (24) • *SOF + DCV + RBV (24)
4	• SOF/VEL (12) • *Peg-IFN + RBV (24/48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • OBV/PTV/RTV + RBV (12) • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12)* • Best supportive care (watchful waiting)	• SOF/VEL^{+} (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (24/48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • *SOF/LDV (12) • OBV/PTV/RTV + RBV (24)[b] • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12)* • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL (12) • *Peg-IFN + RBV (48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • SOF/LDV (12) • OBV/PTV/RTV + RBV (12) • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12/36)* • Best supportive care (watchful waiting)	• SOF/VEL^{+} (12) • *SOF + peg-IFN + RBV (12)* • *Peg-IFN + RBV (48)* • EBR/GZR (12) or + RBV (16) depending on viral titre • *SOF/LDV[a] (12) • OBV/PTV/RTV + RBV (24)[b] • *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12/36)* • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* • Best supportive care (watchful waiting)

Geno-type	Treatment (duration in weeks)			
	TN-NC	**TN-C**	**TE-NC**	**TE-C**
	Treatments only recommended for patients with significant fibrosis[c]: • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]: • *SOF + DCV (12)*	Treatments only recommended for IFN-ineligible patients: • **SOF + DCV ± RBV (24)*	Treatments only recommended for patients with significant fibrosis[c]: • *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)* Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]: • *SOF + DCV (12)*	Treatments only recommended for IFN-ineligible patients: • **SOF + DCV ± RBV (24)*
5 or 6	• SOF/VEL (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL[+] (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)	• SOF/VEL[+] (12) • SOF + peg-IFN + RBV (12) • *Peg-IFN + RBV (24)* • Best supportive care (watchful waiting)

Source: CS, section B1.4, Table 4, pages 27-30[2]

*CC only (i.e. not recommended for DCC)

[+] + RBV if DCC

[a]Recommended only if all the following criteria are met: Child-Pugh class A, platelet count of 75,000/mm^3 or more, no features of portal hypertension, no history of HCV-associated decompensation episode and not previously treated with an NS5A inhibitor; [b]TA365 for OBV/PTV/RTV ± DSV was published before the results from TURQUOISE-III and AGATE-I became available and the NICE recommendation therefore stipulates the use of OBV/PTV/RTV ± DSV with RBV for GT1b patients with CC, and OBV/PTV/RTV + RBV for GT4 CC patients for 24 weeks. Subsequently, TURQUOISE-III demonstrated the efficacy of treatment with OBV/PTV/RTV + DSV for 12 weeks without RBV in GT1b patients with CC,[27] and AGATE-I demonstrated the efficacy of OBV/PTV/RTV + RBV for 12 weeks in GT4 patients with CC.[28] The licence for OBV/PTV/RTV ± DSV now reflects this. Therefore OBV/PTV/RTV + DSV without RBV for 12 weeks is used as the comparator in the economic analysis of this submission for GT1b patients with CC, and OBV/PTV/RTV + RBV for 24 weeks is used for GT4 CC patients; [c]Significant fibrosis is defined as METAVIR fibrosis stage F3 and F4.

BOC = boceprevir; C = cirrhotic; CC = compensated cirrhosis; DCC = decompensated cirrhosis; DCV = daclatasvir; DSV = dasabuvir; EBR = elbasvir; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; peg-IFN = pegylated-IFN; PTV = paritaprevir; RAV = resistance associated variant; RBV = ribavirin; RTV = ritonavir; SMV = simeprevir; SOF = sofosbuvir; TVR = telaprevir; TN = treatment-naïve; TE = treatment-experienced; VEL = velpatasvir

Therapies highlighted in *italics* represent therapies that, although associated with a positive NICE recommendation for use in the NHS, no longer form part of current clinical practice according to the company and are therefore not considered as comparators to G/P in this submission.

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 (TN) • who have had treatment for CHC before (TE)	Per final scope	This is in accordance with the scope.
Intervention	Glecaprevir/pibrentasvir; referred to in this submission as G/P	Per final scope	This is in accordance with the scope.
Comparator(s)	• Best supportive care (no active pharmacological treatment) (GT1-6) • DCV in combination with SOF, with or without RBV (for specific people with GT1, GT3 or GT4; as recommended by NICE) • EBR/GZR (for GT1 or GT4) • SOF/LDV (for specific people with GT1 or GT4; as recommended by NICE) • OBV/PTV/RTV with or without DSV or RBV (for GT1 or GT4) • IFN with RBV (for GT1– 6) • SOF in combination with RBV, with or without pegIFNα (for specific people with GT1–6; as recommended by NICE) • SOF/VEL (for specific people with GT1–6; as recommended by NICE)	• Best supportive care (no active pharmacological treatment) (GT1–6) • DCV in combination with SOF without RBV (for GT3 only, as recommended by NICE) • EBR/GZR (for GT1 or GT4) • SOF/LDV (for specific people with GT1 or GT4; as recommended by NICE) • OBV/PTV/RTV with or without DSV or RBV (for GT1 or GT4) • IFN with RBV for GT2 non-cirrhotic treatment-naïve patients only • SOF in combination with RBV, with or without pegIFNα (for specific people with GT2, GT3, GT5 and GT6, as recommended by NICE) • SOF/VEL (for specific people with GT1–6; as recommended by NICE)	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 watchful waiting/no treatment in their submission. In addition, the following treatments are not included in the CS because these treatment regimens are not used in current NHS practice according to the company: • DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE) • IFN with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients) • SOF in combination with RBV, with or without IFN (for specific

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comments
			people with GT1 and GT4; as recommended by NICE)
Outcomes	The outcome measures to be considered include: • mortality • SVR • development of resistance to treatment • adverse effects of treatment • HRQoL	Per final scope	Mostly in line with the final scope. The development of resistance to G/P treatment (as well as to other comparators) was not incorporated to the electronic model, assuming it has limited impact on the cost effectiveness of G/P.
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Genotype • Co-infection with HIV • People with and without cirrhosis • Previous treatment received (with or without DAA-containing regimens) • People who have received treatment before liver transplantation, and those who have received it after liver transplantation • Response to previous treatment (non-response, partial response, relapsed) • People who are intolerant to or ineligible for interferon treatment • People with and without renal impairment	Clinical evidence for these subgroups is presented where this is available. The economic analyses are stratified by genotype, cirrhosis status and previous treatment history (naïve or experienced), in line with recent prior NICE appraisals. Separate comparators for IFN-eligible and IFN-ineligible subgroups were also considered in line with NICE guidance. Patients co-infected with HCV/HIV-1 are modelled as the same as those with HCV mono-infection. This is consistent with the approach taken in TA430.[1] The analyses split patients into TN and TE, where the TE group was defined as patients who have not adequately responded to prior IFN/RBV-based treatment with or without SOF, in line with the clinical trial programme for G/P and its anticipated licence. Separate economic subgroup analyses are not performed for TE patients stratified by previous treatment response. This is in line with the fact that neither NICE TA guidance nor the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1) provides distinct treatment recommendations on the basis of	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. Separate subgroup analyses are not presented for patients who are co-infected with HIV and those with post-liver transplantation. In addition, separate subgroup analyses are not presented for people who are intolerant to or ineligible for interferon treatment, except for GT2 treatment-naïve patients.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale	ERG comments
		different previous treatment response.[2] Subgroup analyses were not performed in patients who had previously received treatment with NS3/4A- or NS5A inhibitors as G/P is currently not anticipated to be licensed in these patients. Separate economic subgroup analyses were also not performed for patients who have received a liver transplant or for patients with renal impairment. The submission already considers an extensive number of subgroups subdivided by genotype, treatment history and cirrhosis status. Further subgroup analyses were therefore not performed, in order to focus the decision problem on the subgroups defined by genotype, treatment experience and cirrhosis status around which NICE treatment recommendations are based.	
Special considerations including issues related to equity or equality	If the evidence allows, the impact of treatment on reduced onward HCV transmission will also be considered.	Onward transmission is not included in the economic model. Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework.	

Source: Table 1, Section B.1.1 of the CS.[2]

Abbreviations: CHC = chronic hepatitis C; DAA = directly-acting antiviral; DCV = daclatasvir; DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir; GZR = grazoprevir; GT = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; IFN = interferon; LDV = ledipasvir; N/A = not applicable; OBV = ombitasvir; Peg-IFN = pegylated-interferon alfa; PTV = paritaprevir; QALY = quality adjusted life year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response; TA = technology appraisal; TE = treatment-experienced; TN = treatment-naïve; 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-naïve) or who have had treatment for chronic hepatitis C before (treatment-experienced).

On 22 June 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Maviret, (glecaprevir/pibrentasvir) intended for the treatment of chronic hepatitis C in adults.[10]

The population is in line with the NICE scope.

3.2 Intervention

The intervention described in the final scope is glecaprevir/pibrentasvir (G/P). According to the CHMP, Maviret is a fixed dose combination of two direct acting-antivirals (DAA), glecaprevir and pibrentasvir. It will be available as film-coated tablets containing 100 mg glecaprevir and 40 mg pibrentasvir. Glecaprevir is an inhibitor of the HCV NS3/4A protease, while pibrentasvir is an inhibitor of the HCV NS5A protein. Both proteins are essential for HCV replication.[10]

The recommended dose of glecaprevir/pibrentasvir is 300 mg/120 mg (three 100 mg/40 mg tablets), taken orally, once daily with food. The recommended glecaprevir/pibrentasvir treatment durations for patients without prior HCV therapy is eight weeks for patients without cirrhosis and 12 weeks for patients with cirrhosis. Similarly, for patients with genotype 1, 2, 4, 5, or 6 who have failed prior therapy with IFN+RBV +/- SOF or SOF+RBV, the recommended glecaprevir/pibrentasvir treatment duration is eight weeks for patients without cirrhosis and 12 weeks for patients with cirrhosis. For patients with genotype 3 who have failed prior therapy with IFN+RBV +/- SOF, or SOF+RBV, the recommended glecaprevir/pibrentasvir treatment duration is 16 weeks (with or without cirrhosis).[11]

G/P is not recommended for the re-treatment of patients with prior exposure to NS3/4A- and/or NS5A-inhibitors. G/P is contraindicated for patients with severe hepatic impairment (Child-Pugh C).

G/P is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.[11]

3.3 Comparators

The comparators described in the final scope are as follows:

- Best supportive care (no active pharmacological treatment) (GT1-6)
- DCV in combination with SOF, with or without RBV (for specific people with GT1, GT3 or GT4; as recommended by NICE)
- EBR/GZR (for GT1 or GT4)
- SOF/LDV (for specific people with GT1 or GT4; as recommended by NICE)
- OBV/PTV/RTV with or without DSV or RBV (for GT1 or GT4)
- IFN with RBV (for GT1– 6)
- SOF in combination with RBV, with or without IFN (for specific people with GT1–6; as recommended by NICE)
- SOF/VEL (for specific people with GT1–6; as recommended by NICE)

The company made the following changes to the final scope:

- DCV in combination with SOF, with or without RBV was assessed for GT3 only;

- IFN with RBV was assessed for GT2 treatment-naïve patients without cirrhosis only; and
- SOF in combination with RBV, with or without IFN was excluded from the decision problem.

These changes were made based on the company's rationale that these treatment regimens are no longer used in current NHS practice.

ERG comment: The ERG's clinical expert agreed that indeed these treatment regimens were no longer used in NHS clinical practice.

3.4 Outcomes

The CS[2] includes the following outcomes, all of which are specified in the final NICE scope[12]:

- Mortality
- SVR
- Development of resistance to treatment
- Adverse effects of treatment
- HRQoL

The economic model does not include development of resistance to treatment, stating that this outcome does not impact the cost effectiveness of G/P, 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[2] includes consideration of the following subgroups, all of which were specified in the final NICE scope[12]:

- Genotype
- People with and without cirrhosis
- Previous treatment history (naïve or treatment-experienced)

In addition, the company considered separate comparators for IFN-eligible and IFN-ineligible subgroups.

Separate subgroup analyses are not presented for patients who are: co-infected with HIV, previous treatment received (with or without DAA-containing regimens), people who have received treatment before liver transplantation, and those who have received it after liver transplantation, response to previous treatment (non-response, partial response, relapsed), and people with and without renal impairment. The company stated that '*it is not considered feasible to perform subgroup analyses in these special patient populations, given the existing need to stratify all analyses by genotype, cirrhosis status and treatment history, the criteria around which previous NICE treatment recommendations are based.*'[13]

Under 'special considerations including issues related to equity or equality', the company mentioned that the impact of treatment on reduced onward HCV transmission would also be considered if the evidence allowed. However, onward transmission is not included in the economic model because this would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework.

The company is negotiating a pricing agreement with the CMU such that the total regimen cost of G/P is

[redacted]

[redacted]. This is pending acceptance at the time of submission. This is not a PAS but represents a negotiated confidential pricing agreement.

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[14] The submission was also checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[15]

The CS stated that systematic review searches were undertaken in April 2017.[2] Searches were reported in detail in Appendix D for the following databases: PubMed, Embase, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CENTRAL).[16] In response to clarification, the company reran Embase, PubMed and Cochrane Library searches in August 2017.[17]

Additional searches of the following conference proceedings were reported for the last two years: American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), The Viral Hepatitis Congress and Asian Pacific Association for the Study of the Liver.

ERG comment:

- The database searches were clearly structured (population, intervention, study design), using a combination of subject heading indexing and free text terms, with synonyms, adjacency operators and truncation. Publication year was limited from 2004 onwards and there were no language limits.
- The original clinical effectiveness search undertaken in Embase was limited to results with "clinical trial" in the title and abstract only. To correct this, the company repeated the search but did not include a number of comparators in the updated search that had been included in the original search, specifically RBV and peg-IFN alpha, as per the decision problem addressed in the CS.[2] The omission of these comparators in the updated search and the "clinical trial" limitation in the first search may mean that relevant information has been missed.
- In response to the clarification letter, the company reported the search strategy undertaken for the conference searches. However, the conference searches did not include terms for G/P (the intervention of interest) or a number of comparators indicated in the decision problem: RBV, peg-IFN alpha and RTV. It is a possibility that relevant evidence has therefore been missed.
- In response to a typographical error in the original PubMed searches, the company reran the hepatitis C search terms to include the MeSH heading "hepacvirus". Unfortunately, the company did not rerun the original hepatitis C search terms to compare against, so were unable to detect any additional articles which may have been found with the corrected MeSH heading for "hepacvirus". The ERG did not recognise the search syntax used in the updated PubMed search, so were not able to replicate the search to ensure nothing had been missed.
- In response to the ERG's concern that study design filters had been applied to searches in the Cochrane Library, which is a study design-specific resource, the company reran the searches to disregard the clinical trials filter. The additional records retrieved were screened but did not yield anything significant.

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 Appendix D, Table 121, page 14).

Table 4.1: Eligibility criteria used in the search strategy

PICOS	Inclusion and exclusion criteria
Population	• Adult patients (≥18 years of age) of any race and gender • Patients were chronically infected with HCV GT1–6 • Studies which assessed mixed populations were included only if outcomes were reported for the relevant population • Studies in which patients were not chronically infected with HCV GT1–6 were excluded • Studies with renal, transplant or HCV-HIV co-infected patients were excluded
Interventions	• IFN-free regimens, including: G/P, SOF/VEL, EBR/GZR ± RBV, SOF/LDV ± RBV, OBV/PTV/RTV ± DSV ± RBV, SOF + DCV ± RBV, SOF + RBV • IFN-containing regimens: DCV + peg-IFN + RBV, SMV + peg-IFN + RBV, SOF + peg-IFN + RBV • Interventions using other DAA combinations, with or without peg-IFN and RBV were excluded, as well as studies which assessed only peg-IFN and/or RBV and other experimental DAAs not listed in the inclusion criteria.
Comparator(s)	All
Outcomes	SVR12, SVR24, DAE, OAE, safety outcomes (including but not limited to: anaemia, pruritus, nausea, neutropaenia, rash and thrombocytopenia)
Study design	• Randomised controlled trials and controlled trials with at least one arm assessing an intervention of interest • Non-randomised clinical trials, including single-arm prospective clinical trials assessing an intervention of interest • Comments, editorials or review articles were excluded, as well as Meta-analysis, Phase I studies or *in vitro* studies and Observational or retrospective studies
Language restrictions	• Only articles in the English language were included

Source: Table 121 of the CS appendix, page 14
DAA = direct-acting antiviral; DAE = discontinuations relating to adverse events; DCV = daclatasvir; DSV = dasabuvir; EBR/GZR = elbasvir/grazoprevir; G/P = glecaprevir/pibrentasvir; GT = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN = interferon; LDV = ledipasvir; OAE = overall adverse events; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; VEL = velpatasvir

ERG comment: These inclusion criteria match the decision problem set out within the final NICE scope[12] in terms of the population and the intervention. 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 2004 date cut-off was applied. This is mentioned on page 4 of the CS, Appendix D (search strategy).

The inclusion criteria state that randomised clinical trials and non-randomised clinical trials, including single-arm prospective clinical trials assessing an intervention of interest, were included. This is appropriate as the company performed a naïve comparison using individual arms of studies. However, the company used a trial filter in their search strategy which may well have excluded most single arm studies. For the proposed analysis, limiting the inclusion criteria to randomised trials only makes no sense. Therefore, for the naïve comparison, relevant studies may have been missed.

The study selection process was provided in a flow diagram of study selection (see CS Appendix D, Figure 17, page 15) that indicates that 81 publications (reporting on 79 studies) were identified as meeting the eligibility criteria. Fourteen of these publications, representing seven studies, involved G/P.[18-30]

In addition, information on four further clinical studies of G/P in patients with CHC are included in the company submission (EXPEDITION-2, EXPEDITION-4, MAGELLAN-I, MAGELLAN-II). These studies were conducted in special populations of patients with HIV co-infection, renal impairment, failure on prior DAAs and a post-transplant population, respectively. The company clarified that these trials were undertaken by AbbVie and identified from company records of the clinical development programme. The company considered that these trials would provide supportive data on the efficacy of G/P. The results from these studies have been published,[31-37] but were not identified by the SLR, since trials in special populations were excluded under the SLR eligibility criteria (see above). This means no comparative data are presented in the CS for these populations.

Finally, the company mentions two trials in Japanese patients with CHC: CERTAIN-1 and CERTAIN-2. These trials are only minimally discussed in the CS and not included in the economic model because "*these two trials were conducted entirely in Japanese patients*" which "*precludes their generalisability to the UK patient population and subsequently their use in the economic model*", according to the company.

A summary of the studies providing evidence for G/P is provided in Table 4.2 below.

Table 4.2: Clinical effectiveness evidence: G/P studies

Study acronym	Intervention(s)	Comparator(s)	Population	Notes
ENDURANCE studies				
ENDURANCE-1[18, 38, 39]	G/P (300 mg/120 mg OD) for 8 or 12 weeks	None	• GT1 • TN or TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN (TE-PRS) • NC • With or without HIV-1 co-infection	
ENDURANCE-2[19, 40, 41]	G/P (300 mg/120 mg OD) for 12 weeks	Placebo	• GT2 • TN or TE-PRS • NC	Not used in economic model. Treatment duration not in line with anticipated licence for NC patients.

Study acronym	Intervention(s)	Comparator(s)	Population	Notes
ENDURANCE-3[20, 42, 43]	G/P (300 mg/120 mg OD) for 8 or 12 weeks	SOF + DCV for 12 weeks	• GT3 • TN • NC	Multicentre, randomised, open-label, active-controlled, Phase III
ENDURANCE-4[21, 44, 45]	G/P (300 mg/120 mg OD) for: 12 weeks	None	• GT4, GT5 or GT6 • TN or TE-PRS • NC	Not used in economic model. Treatment duration not in line with anticipated licence for NC patients.
EXPEDITION-1 and SURVEYOR-II, Parts 2 and 3				
EXPEDITION-1)[46, 47]	G/P (300 mg/120 mg OD) for 12 weeks	None	• GT1, GT2, GT4, GT5 or GT6 • TN or TE-PRS • CC	
SURVEYOR-II, Part 2[22, 23, 48-52]	G/P (300 mg/120 mg OD) for 8 or 12 weeks ± RBV	None	• GT2, GT3 • TN or TE with regimens containing peg-IFN/RBV (TE-PR) • NC or CC (GT3 CC were TN only[a]; GT2 were NC only)	
SURVEYOR-II, Part 3[24, 48, 51, 52]	G/P (300 mg/120 mg OD) for 12 or 16 weeks	None	• GT3 • TN CC • TE-PRS NC CC	
SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 studies				
SURVEYOR-I, Part 2[23, 49, 53-55]	G/P (300 mg/120 mg OD) for 8 or 12 weeks	None	• GT1, GT4, GT5 or GT6 • TN or TE-PR • GT1 NC and CC; GT4, GT5 and GT6 NC only	Not used in economic model. Data from larger trials were available.
SURVEYOR-II, Part 1[48, 49, 51, 52, 56]	G/P (300 mg/120 mg OD or 200mg/120 mg OD) for 12 weeks ± RBV	None	• GT2, GT3 • TN or TE-PR • NC	
SURVEYOR-II, Part 4[48, 51, 52, 57]	G/P (300 mg/120 mg OD) for 8 weeks	None	• GT2, GT4, GT5 or GT6 • TN or TE-PRS • NC	

Study acronym	Intervention(s)	Comparator(s)	Population	Notes
EXPEDITION-2 and 4 and MAGELLAN studies				
EXPEDITION-2[32, 58]	G/P (300 mg/120 mg OD) for 8 (NC, n=137)) or 12 (CC, n=16) weeks	None	• GT1, GT2, GT3, GT4, GT5 or GT6 • TN or TE • NC or CC • With HIV co-infection	Not used in economic model. Only limited details are presented; trial has only recently been completed
EXPEDITION-4[34, 59, 60]	G/P (300 mg/120 mg OD) for 12 weeks	None	• GT1, GT2, GT3, GT4, GT5 or GT6 • TN (all genotypes) or TE-PRS (GT1, GT2, GT4, GT5 or GT6) • NC or CC • Who had severe renal impairment or end-stage renal disease (including those on dialysis)	Not used in economic model. A subgroup analysis for patients with severe renal impairment was not performed
MAGELLAN-I, Part 1[31, 35, 61, 62]	G/P (300 mg/120 mg OD) for 12 weeks ± RBV	None	• GT1 • TE-DAA • NC	Not used in economic model. Population is not within the anticipated licence for G/P
MAGELLAN-I, Part 2)[31, 36, 37, 61, 62]	G/P (300 mg/120 mg OD) for 12 or 16 weeks	None	• GT1, GT4, GT5 or GT6 • TE-DAA • NC or CC	Not used in economic model.
MAGELLAN-II[33, 62, 63]	G/P (300 mg/120 mg OD) for 12 weeks	None	• GT1, GT2, GT3, GT4, GT5 or GT6 • TN or TE • NC • Patients who had received a liver or renal transplant.	Not used in economic model. Only limited details are presented; trial has only recently been completed.
CERTAIN studies				
CERTAIN-1, part 1[64-66]	G/P (300 mg/120 mg OD) for 8 weeks	OBV/PTV/RTV	• GT1 • NR • NC	Not used in economic model. Japanese adults with CHC Part 1: All patients with Y93H polymorphisms received 8 weeks G/P
CERTAIN-1, part 2[64-66]	G/P (300 mg/120 mg OD) for 8 or 12 weeks	None	• GT1, GT2, GT3, GT4, GT5, GT6 • TE-DAA • CC or NC	

Study acronym	Intervention(s)	Comparator(s)	Population	Notes
			• Patients with severe renal impairment and CC	
CERTAIN-2[64, 67-69]	G/P (300 mg/120 mg OD) for 8 weeks	SOF + RBV for 12 weeks	• GT2 • DAA-TN • NC • Patients with severe renal impairment and CC	Not used in economic model. Japanese adults with CHC

Source: CS, Tables 6-9, pages 38-44.
CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; NC, non-cirrhotic; OD, once daily; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-DAA = TE with regimens containing DAAs; TE-PRS = TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve.
[a]When SURVEYOR-II, Part 2 enrolment was initiated, both TN and TE-PR CC GT3-infected patients were eligible for enrolment, but after 7 TE-PR CC GT3-infected patients were enrolled, enrolment was halted for these patients based on feedback from the United States Food and Drug Administration.

4.1.3 Critique of data extraction

The data extraction process was not described and it is not stated how many reviewers were involved in the data extraction process.

ERG comment: The involvement of two reviewers in the data extraction of included studies helps to reduce the potential for bias and error. It is usual to report data extraction methods including details of how many reviewers were involved and processes for resolving discrepancies. Without this detail, it is impossible to exclude the risk of bias in the review.

4.1.4 Quality assessment

Tables 133 to 140 in the CS, Appendix D.2 (pages 88-99) provided an overview of the quality assessment of the G/P studies. For randomised controlled trials, quality assessment was performed using the quality assessment tool based on the CRD's guidance for undertaking reviews in healthcare, as recommended by NICE. For non-RCTs, the Downs and Black checklist was used.[70]

ERG comment: Using different quality assessment tools for RCTs and non-RCTs is unusual in this case, as only single arms from studies were included in the CS. Therefore, the distinction between RCTs (usually the gold standard) and other study designs is irrelevant. Observational data from included studies were used for comparative analyses between studies. These types of data are not suitable for comparative purposes. Therefore, the quality of all included studies is poor.

4.1.5 Evidence synthesis

Regarding evidence synthesis of G/P evidence, the company states that (CS, Section B2.9, page 130): "As the G/P trials presented do not provide direct evidence in comparison to all the relevant comparators in this submission, meta-analyses are not presented and the approach taken to comparative effectiveness is detailed in Section B.2.10."

ERG comment: The ERG agrees that a meta-analysis of G/P studies is not feasible. For a critique of the 'approach taken to comparative effectiveness', please see Section 4.4 of this report.

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, seven G/P studies were identified through the search strategy and four further clinical trials of G/P in patients with CHC are included in the company submission. We will describe those G/P studies that had treatment durations that were in line with the anticipated licence indication for the population included in the study and were used in the economic model (see Table 4.3). Trial methodology for these studies is reported in Tables 4.4 and 4.5 and baseline characteristics are reported in Table 4.6.

Only one of these studies included an active comparator: ENDURANCE-3. However, ENDURANCE-3 included three arms (G/P-12w, SOF+DCV-12w and G/P-8w) and patients were only randomised to two of the three arms: G/P-12w versus SOF+DCV-12w. After enrolment in these two arms was complete, new patients were assigned to receive G/P for eight weeks. Therefore, G/P-8w is not part of the randomised comparison and G/P-12w is not in line with the anticipated licence for patients in this trial. This means there is no direct comparative evidence for G/P versus any of the comparators mentioned in the scope, apart from the two CERTAIN trials. Since the CERTAIN trials were in Japanese patients only, these were considered by the company as not generalisable to the UK population.

ERG comment: We asked our clinical experts whether it was reasonable to exclude the CERTAIN studies and the response was mixed. On the one hand, there is no reason to assume that the relative effectiveness of G/P versus other active comparators would be different in a Japanese population; on the other hand, given the SVR rates reported in the CERTAIN studies, including these would probably not make any difference. Therefore, we have not reported the CERTAIN studies in the main part of our report; however, we have reported a summary of both studies in Section 4.5.

Table 4.3: G/P studies with data used in the economic model

Trial no. (acronym)	Intervention(s)	Comparator(s)	Population
ENDURANCE studies			
ENDURANCE -1[18, 38, 39]	G/P (300 mg/120 mg OD) for 8 or 12 weeks	None	• GT1 • TN or TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN (TE-PRS) • NC • With or without HIV-1 co-infection
ENDURANCE -3[20, 42, 43]	G/P (300 mg/120 mg OD) for 8 or 12 weeks	SOF + DCV for 12 weeks	• GT3 • TN • NC
EXPEDITION-1 and SURVEYOR-II studies			
EXPEDITION-1)[46, 47]	G/P (300 mg/120 mg OD) for 12 weeks	None	• GT1, GT2, GT4, GT5 or GT6 • TN or TE-PRS • CC
SURVEYOR-II, Part 1[48, 49, 51, 52, 56]	G/P (300 mg/120 mg OD or 200mg/120 mg OD) for 12 weeks ± RBV	None	• GT2, GT3 • TN or TE-PR • NC

Trial no. (acronym)	Intervention(s)	Comparator(s)	Population
SURVEYOR-II, Part 2[22, 23, 48-52]	G/P (300 mg/120 mg OD) for 8 or 12 weeks ± RBV	None	• GT2, GT3 • TN or TE with regimens containing peg-IFN/RBV (TE-PR) • NC or CC (GT3 CC were TN only[a]; GT2 were NC only)
SURVEYOR-II, Part 3[24, 48, 51, 52]	G/P (300 mg/120 mg OD) for 12 or 16 weeks	None	• GT3 • TN CC • TE-PRS NC CC
SURVEYOR-II, Part 4[48, 51, 52, 57]	G/P (300 mg/120 mg OD) for 8 weeks	None	• GT2, GT4, GT5 or GT6 • TN or TE-PRS • NC

Source: CS, Tables 6-9, pages 38-44.

CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; NC, non-cirrhotic; OD, once daily; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-DAA = TE with regimens containing DAAs; TE-PRS = TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve.

[a]When SURVEYOR-II, Part 2 enrolment was initiated, both TN and TE-PR CC GT3-infected patients were eligible for enrolment, but after 7 TE-PR CC GT3-infected patients were enrolled, enrolment was halted for these patients based on feedback from the United States Food and Drug Administration.

Table 4.4: Summary of trial methodology for relevant G/P studies (ENDURANCE and EXPEDITION)

Trial acronym	ENDURANCE-1[18, 38, 39]	ENDURANCE-3[20, 42, 43]	EXPEDITION-1[46, 47]
Clinicaltrials.gov identifier	NCT02604017	NCT02640157	NCT02642432
Study population	GT1, TN or TE-PRS, NC G/P treatment length: 8 or 12 weeks With or without HIV-1 co-infection	GT3, TN, NC G/P treatment length: 8 or 12 weeks	GT1, GT2, GT4-6, TN or TE-PRS, CC G/P treatment length: 12 weeks
Study objective	To compare the efficacy of 8- versus 12-week treatment with G/P.	To compare the efficacy of 12-week treatment with G/P versus 12-week treatment with SOF + DCV and versus 8-week treatment with G/P.	To evaluate the efficacy of 12-week treatment with G/P.
Location	110 study locations in the United States, Australia, Austria Belgium, Canada, Chile, France, Germany, Hungary, Israel, Italy, Korea, Lithuania, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Spain, Sweden, Switzerland and Taiwan, and 6 sites (28 patients) in the United Kingdom	69 study locations in the United States, Australia, Canada, France, Germany, New Zealand, Sweden and Switzerland, and 9 sites (81 patients) in the United Kingdom	40 study locations in the United States, Belgium, Canada, Germany, South Africa and Spain
Trial design	Multicentre, randomised, open-label, Phase III	Multicentre, partially randomised, open-label, active-controlled, Phase III	Multicentre, open-label, single-arm, Phase III
Duration of study	Treatment duration: 8 or 12 weeks depending on treatment assignment Follow-up: up to 24 weeks post-treatment	Treatment duration: 8 or 12 weeks depending on treatment assignment Follow-up: up to 24 weeks post-treatment	Treatment duration: 12 weeks Follow-up: up to 24 weeks post-treatment
Intervention(s) (n=) and comparators(s) (n=)	Patients receiving G/P received three fixed-dose combination tablets containing 100 mg of GLE and 40 mg of PIB OD Patients were randomised in a 1:1 ratio to: G/P for 12 weeks (n=352) G/P for 8 weeks (n=351)	Patients were randomised in a 2:1 ratio to: G/P for 12 weeks (n=233) SOF + DCV for 12 weeks (n=115)	G/P for 12 weeks (n=146)

Trial acronym	ENDURANCE-1[18, 38, 39]	ENDURANCE-3[20, 42, 43]	EXPEDITION-1[46, 47]
		After enrolment in these two arms was complete, new patients were assigned to receive G/P for 8 weeks (n=157) Patients receiving SOF + DCV received one 400 mg tablet of SOF and one 60 mg tablet of DCV OD	
Permitted and disallowed concomitant medication	Patients were on a stable dose of concomitant medications, which were confirmed to be safely administered with study drugs, for at least 2 weeks prior to initiation of study drugs. Patients were required to discontinue the prohibited medications and supplements listed below at least 2 weeks or 10 half-lives (whichever was longer) prior to the first dose of any study drug, and were not allowed to use these during the treatment period and for 30 days following discontinuation of study drugs Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin Atorvastatin, lovastatin, simvastatin Astemizole, cisapride, terfenadine Ethinyl estradiol containing oral contraceptives and systemic immunosuppressants Patients were allowed to resume previously prohibited medications/supplements or revert to pre-study doses, 30 days following discontinuation of study drugs		
Primary outcomes (including scoring methods and timings of assessments)	SVR12 is defined as HCV RNA <LLOQ at 12 weeks after EOT Non-inferiority of the percentage of patients achieving SVR12 in the 12-week arm ITT mono-infected GT1 DAA-naïve (ITT-PS) population compared to the historical efficacy established by current approved SoC regimens for this patient population (OBV/PTV/RTV + DSV ± RBV or SOF/LDV for 12 weeks) Non-inferiority of the percentage of patients achieving SVR12 in the 8-week arm compared to the 12-week arm in the per	Non-inferiority of the percentage of patients in the ITT population achieving SVR12 in the G/P 12-week arm compared to the SOF + DCV 12-week arm Non-inferiority of the percentage of patients in the ITT population achieving SVR12 in the G/P 8-week arm compared to the G/P 12-week arm Safety	Percentage of patients in the ITT population achieving SVR12, as defined as HCV RNA <LLOQ at 12 weeks after EOT Safety

Trial acronym	ENDURANCE-1[18, 38, 39]	ENDURANCE-3[20, 42, 43]	EXPEDITION-1[46, 47]
	protocol ITT mono-infected GT1 DAA-naïve (ITT-PS-PP) population Non-inferiority of the percentage of patients achieving SVR12 in the 8-week arm compared to the 12-week arm in ITT mono-infected GT1 DAA-naïve (ITT-PS) population		
Pre-planned subgroups	When study arms were not divided by patient characteristics such as treatment or cirrhosis status, post-hoc analyses were performed to examine the results in these subgroups		When study arms were not divided by patient characteristics such as treatment or cirrhosis status, post-hoc analyses were performed to examine the results in these subgroups

Source: CS, Table 11 and 12, page 53-59

DAA = direct-acting antiviral; DB = double-blind; DCV = daclatasvir; DSV = dasabuvir; EOT = end of treatment; EQ-5D-3L = EuroQol-5 Dimensions-three Level; FSS = Fatigue Severity Scale; G/P = glecaprevir/pibrentasvir; GLE = glecaprevir; GT = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN = interferon; IRT = interactive response technology; ITT = intention-to-treat; ITT-MS = ITT mono-infected HCV GT1 population; ITT-PS = ITT mono-infected GT1 DAA-naïve; ITT-PS-PP = per-protocol ITT-PS; IU = infectious unit; LLOQ = lower limit of quantitation; NC = non-cirrhotic; NGS = next generation sequencing; OBV = ombitasvir; OD = once-daily; OL = open-label; peg-IFN = pegylated IFN; PIB = pibrentasvir; PRO = patient reported outcome; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SF-36v2 = SF-36 version 2; SoC = standard of care; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TE-PRS = treatment-experienced with regimens containing IFN = peg-IFN ± RBV = SOF + RBV ± peg-IFN; TN = treatment-naïve; WPAI-HCV = Work Productivity Activity Impairment Hepatitis C Specific Instrument

Table 4.5: Summary of trial methodology for relevant G/P studies (SURVEYOR-II)

Trial acronym	SURVEYOR-II, Part 1[48, 49, 51, 52, 56]	SURVEYOR-II, Part 2[22, 23, 48-52]	SURVEYOR-II, Part 3[24, 48, 51, 52]	SURVEYOR-II, Part 4[48, 51, 52, 57]
Clinicaltrials.gov identifier	NCT02243293			
Study population	GT2, GT3 TN or TE-PRS, NC G/P treatment length: 12 weeks ± RBV	GT2, GT3, TN or TE-PR, NC or CC G/P treatment length: 8 or 12 weeks ± RBV	GT3, TN CC, TE-PRS NC or CC G/P treatment length: 12 or 16 weeks	GT2, GT4-6, TN or TE-PRS, NC G/P treatment length: 8 weeks
Study objective	To evaluate the efficacy of 12-week G/P treatment	To evaluate the efficacy of 8- or 12-week G/P treatment	To evaluate the efficacy of 12- or 16-week G/P treatment	To compare the efficacy of 8-week treatment with G/P versus the historical efficacy of 12-week treatment with SOF + RBV
Location	For whole SURVEYOR-II study: 78 study locations in the United States, Australia, Canada, France, Korea, New Zealand and Taiwan, and 3 sites in the United Kingdom			
	No patients in the UK were enrolled in Part 1	4 patients in the UK were enrolled in Part 2	5 patients in the UK were enrolled in Part 3	No patients in the UK were enrolled in Part 4
Trial design	Multicentre, randomised, open-label, Phase II	Multicentre, partially-randomised open-label, Phase II		Multicentre, open-label, single-arm, Phase II
Duration of study	Treatment duration: 12 weeks Follow-up: up to 24 weeks post-treatment	Treatment duration: 8 or 12 weeks depending on treatment assignment Follow-up: up to 24 weeks post-treatment	Treatment duration: 12 or 16 weeks depending on treatment assignment Follow-up: up to 24 weeks post-treatment	Treatment duration: 8 weeks Follow-up: up to 24 weeks post-treatment
Intervention(s) (n=) and comparators(s) (n=)	Patients receiving G/P received three 100 mg tablets of GLE and three 40 mg tablets of PIB OD unless otherwise stated			
	GT2 NC patients were randomised in a 1:1:1 ratio to: G/P (300 mg/120 mg) for 12 weeks (n=25)	In this trial patients receiving G/P received three 100 mg tablets of GLE and three 40 mg tablets of PIB OD	TE-PRS patients without cirrhosis were randomised at a 1:1 ratio to: G/P for 12 weeks (n=22)	Patients in this study received three fixed-dose combination tablets containing 100 mg of GLE and 40 mg of PIB OD G/P for 8 weeks

Trial acronym	SURVEYOR-II, Part 1[48, 49, 51, 52, 56]	SURVEYOR-II, Part 2[22, 23, 48-52]	SURVEYOR-II, Part 3[24, 48, 51, 52]	SURVEYOR-II, Part 4[48, 51, 52, 57]
	G/P (200 mg/120 mg) for 12 weeks (n=24) G/P (200 mg/120 mg) + RBV for 12 weeks (n=25) Patients receiving RBV received 1,000 mg or 1,200 mg (weight based) divided twice daily GT3 NC patients were randomised in a 1:1:1:1 ratio to: G/P (300 mg/120 mg) for 12 weeks (n=30) G/P (200 mg/120 mg) for 12 weeks (n=31) G/P (200 mg/120 mg) + RBV for 12 weeks (n=31) G/P (200 mg/40 mg) for 12 weeks (n=30)	GT2 NC patients were enrolled to receive G/P for 8 weeks (n=54) GT3 NC patients were enrolled to receive G/P for 8 (TN) or 12 (TE-PR) weeks (n=53) GT3 TN CC patients were randomised in a 1:1 ratio to: G/P for 12 weeks (n=28)[a] G/P + RBV for 12 weeks (n=27)[a] Patients receiving RBV received 800 mg OD	G/P for 16 weeks (n=22) TN patients with cirrhosis were only enrolled to receive G/P for 12 weeks (n=40) TE-PRS patients with cirrhosis were only enrolled to receive G/P for 16 weeks (n=47)	GT2 (n=145) GT4, GT5 or GT6 (n=58)
Permitted and disallowed concomitant medication	Patients were on a stable dose of concomitant medications, which were confirmed to be safely administered with study drugs, for at least 2 weeks prior to initiation of study drugs. Patients were required to discontinue the prohibited medications and supplements listed below at least 2 weeks or 10 half-lives (whichever was longer) prior to the first dose of any study drug, and were not allowed to use these during the treatment period and for 30 days following discontinuation of study drugs • Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort • Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin • Atorvastatin, lovastatin, simvastatin • Astemizole, cisapride, terfenadine • Ethinyl estradiol containing oral contraceptives and systemic immunosuppressants			

Trial acronym	SURVEYOR-II, Part 1[48, 49, 51, 52, 56]	SURVEYOR-II, Part 2[22, 23, 48-52]	SURVEYOR-II, Part 3[24, 48, 51, 52]	SURVEYOR-II, Part 4[48, 51, 52, 57]
	• Patients were allowed to resume previously prohibited medications/supplements or revert to pre-study doses, 30 days following discontinuation of study drugs			
Primary outcomes (including scoring methods and timings of assessments)	Percentage of patients in the ITT population achieving SVR12. SVR12 is defined as HCV RNA <LLOQ at 12 weeks after EOT ***SURVEYOR-II, Part 4 only:*** Non-inferiority of the percentage of GT2 DAA-TN NC patients in the ITT population achieving SVR12 compared to the historical efficacy (SVR12 95%) of 12-week treatment with SOF + RBV Safety			
Pre-planned subgroups	When study arms were not divided by patient characteristics such as treatment or cirrhosis status, post-hoc analyses were performed to examine the results in these subgroups			

Source: CS, Table 12 and 13, page 59-67

CC = compensated cirrhosis; DAA = direct-acting antiviral; DB = double-blind; DCV = daclatasvir; DSV = dasabuvir; EOT = end of treatment; EQ-5D-3L = EuroQol-5 Dimensions-three Level; EQ-5D-5L = EuroQol-5 Dimensions-five Level; FSS = Fatigue Severity Scale; G/P = glecaprevir/pibrentasvir; GLE = glecaprevir; GT = genotype; HCV = hepatitis C virus; HCVTSat = chronic HCV treatment satisfaction instrument; HIV = human immunodeficiency virus; IFN = interferon; IRT = interactive response technology; ITT = intention-to-treat; ITT-MS = ITT mono-infected HCV GT1 population; ITT-PS = ITT mono-infected GT1 DAA-naïve; ITT-PS-PP = per-protocol ITT-PS; IU = infectious unit; LLOQ = lower limit of quantitation; NC = non-cirrhotic; NGS = next generation sequencing; OBV = ombitasvir; OD = once-daily; OL = open-label; peg-IFN = pegylated IFN; PIB = pibrentasvir; PRO = patient reported outcome; PTV = paritaprevir; RBV = ribavirin; RNA = ribonucleic acid; RTV = ritonavir; SF-36v2 = SF-36 version 2; SoC = standard of care; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TE-PR = treatment-experienced with regimens containing peg-IFN/RBV; TE-PRS = treatment-experienced with regimens containing IFN = peg-IFN ± RBV = SOF + RBV ± peg-IFN; TN = treatment-naïve; WPAI-HCV = Work Productivity Activity Impairment Hepatitis C Specific Instrument

Table 4.6: Baseline characteristics for relevant G/P studies (ENDURANCE and EXPEDITION)

	ENDURANCE-1[18, 39]	**ENDURANCE-3[20, 43]**	**EXPEDITION-1[47]**
Baseline characteristics, n (%)	G/P 8 weeks (N=351)	G/P 8 weeks (N=157)	G/P 12 weeks (N=146)
Age (years)			
Category 1: <65	309 (88.0)	[redacted]	[redacted]
Category 1: ≥65	42 (12.0)	[redacted]	[redacted]
Category 2: <75	346 (98.6)	[redacted]	[redacted]
Category 2: ≥75	5 (1.4)	[redacted]	[redacted]
Male	167 (47.6)	92 (58.6)	90 (61.6)
BMI (kg/m^2) <30	300 (85.5)	[redacted]	[redacted]
BMI (kg/m^2) ≥30	51 (14.5)	[redacted]	[redacted]
Race			
White	289 (82.3)	134 (85.4)	120 (82.2)
Black	14 (4.0)	[redacted]	[redacted]
Asian	44 (12.5)	[redacted]	[redacted]
Other	4 (1.2)	[redacted]	[redacted]
Baseline fibrosis stage			
F0–F1	296 (85.1)	122 (77.7)	-
F2	22 (6.3)	8 (5.1)	-
F3	30 (8.6)	27 (17.2)	-
F4	0	0	-
Missing	3	-	-
Baseline Child-Pugh score			
5	-	-	[redacted]
6	-	-	[redacted]
>6	-	-	[redacted]

	ENDURANCE-1[18, 39]	**ENDURANCE-3[20, 43]**	**EXPEDITION-1[47]**
Baseline characteristics, n (%)	G/P 8 weeks (N=351)	G/P 8 weeks (N=157)	G/P 12 weeks (N=146)
Missing	-	-	[redacted]
Prior HCV treatment history			
Naïve	219 (62.4)	157 (100)	110 (75.3)
Experienced	132 (37.6)	N/A	36 (24.7)
Type of previous regimen			
IFN-based	131 (37.3)	N/A	[redacted]
SOF-based	1 (0.3)	N/A	[redacted]
Response to previous HCV treatment			
Breakthrough/on-treatment non-responder	[redacted]	N/A	[redacted]
Post-treatment relapse	[redacted]	N/A	[redacted]
Unknown/other	[redacted]	N/A	[redacted]
IL28B genotype			
CC	102 (29.1)	[redacted]	[redacted]
CT	197 (56.1)	[redacted]	[redacted]
TT	52 (14.8)	[redacted]	-
Baseline HCV RNA level (IU/mL)			
Category 1: <6,000,000	302 (86.0)	[redacted]	-
Category 1: ≥6,000,000	49 (14.0)	[redacted]	-
Category 2: <10,000,000	335 (95.4)	[redacted]	-
Category 2: ≥10,000,000	16 (4.6)	[redacted]	-
Other characteristics			
HCV mono-infected	336 (95.7)	157 (100)	-
HCV/HIV-1 co-infected	15 (4.3)	-	-

	ENDURANCE-1[18, 39]	ENDURANCE-3[20, 43]	EXPEDITION-1[47]
Baseline characteristics, n (%)	G/P 8 weeks (N=351)	G/P 8 weeks (N=157)	G/P 12 weeks (N=146)
HCV genotype			
1 (total)	[redacted]	-	87 (59.6)
1a	152 (43.3)	-	[redacted]
1b	[redacted]	-	[redacted]
2 (total)	-	-	34 (23.3)
3 (total)	-	115 (100)	-
4 (total)	-	-	16 (11.0)
5 (total)	-	-	2 (1.4)
6 (total)	-	-	7 (4.8)

Source: CS, Tables 16, 17, 20 and 21, pages 75-89.
CC = compensated cirrhosis; DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; SOF = sofosbuvir; HCV = hepatitis C virus; NC = non-cirrhotic; RBV = ribavirin

Table 4.7: Baseline characteristics for relevant G/P studies (SURVEYOR-II)

	SURVEYOR-II, Part 1[48, 49, 52, 56]		**SURVEYOR-II, Part 2**[23, 49, 53, 55]		**SURVEYOR-II, Part 3**[24, 48, 52]		**SURVEYOR-II, Part 4**[24, 48, 52]
Baseline characteristics, n (%)	GT2 G/P (300 mg/120 mg) 12 weeks, N=25	GT3 G/P (300 mg/120 mg) 12 weeks, N=30	GT2 G/P 8 weeks, N=54	GT3 G/P 12 or 16 weeks, N=28	TN CC G/P 12 weeks, N=40	TE-PRS CC G/P 16 weeks, N=47	GT2 G/P 8 weeks, N=145[a]
Age (years)							
Category 1: <65	21 (84.0)	28 (93.3)	44 (81.5)	[redacted]	38 (95.0)	39 (83.0)	128 (88.3)
Category 1: ≥65	4 (16.0)	2 (6.7)	10 (18.5)	[redacted]	2 (5.0)	8 (17.0)	17 (11.7)
Category 2: <75	-	-	-	-	-	-	-
Category 2: ≥75	-	-	-	-	-	-	-
Male	16 (64.0)	19 (63.3)	33 (61.1)	15 (53.6)	24 (60.0)	36 (76.6)	61 (42.1)
BMI (kg/m^2) <30	15 (60.0)	24 (80.0)	43 (79.6)	[redacted]	25 (62.5)	34 (72.3)	100 (69.0)
BMI (kg/m^2) ≥30	10 (40.0)	6 (20.0)	11 (20.4)	[redacted]	15 (37.5)	13 (27.7)	45 (31.0)
Race							
White	22 (88.0)	29 (96.7)	51 (94.4)	[redacted]	37 (92.5)	42 (89.4)	120 (82.8)
Black	2 (8.0)	1 (3.3)	1 (1.9)	[redacted]	0	0	11 (7.6)
Asian	1 (4.0)	0	0	[redacted]	1 (2.5)	3 (6.4)	10 (6.9)
Other	0	0	2 (3.7)	[redacted]	2 (5)	2 (4.2)	4 (2.8)
Baseline fibrosis stage							
F0–F1	16 (64.0)	18 (60.0)	45 (83.3)	[redacted]	0	0	123 (84.8)
F2	6 (24.0)	6 (20.0)	6 (11.1)	[redacted]	0	0	9 (6.2)
F3	3 (12.0)	6 (20.0)	3 (5.6)	[redacted]	0	0	13 (9.0)
F4	0	0	0	[redacted]	40 (100)	47 (100)	0
Missing	-	-	-	-	-	-	-
Baseline Child-Pugh score							
5	-	-	-	[redacted]	[redacted]	[redacted]	-

	SURVEYOR-II, Part 1[48, 49, 52, 56]		**SURVEYOR-II, Part 2**[23, 49, 53, 55]		**SURVEYOR-II, Part 3**[24, 48, 52]		**SURVEYOR-II, Part 4**[24, 48, 52]
Baseline characteristics, n (%)	GT2 G/P (300 mg/120 mg) 12 weeks, N=25	GT3 G/P (300 mg/120 mg) 12 weeks, N=30	GT2 G/P 8 weeks, N=54	GT3 G/P 12 or 16 weeks, N=28	TN CC G/P 12 weeks, N=40	TE-PRS CC G/P 16 weeks, N=47	GT2 G/P 8 weeks, N=145[a]
6	-	-	-	[redacted]	[redacted]	[redacted]	-
>6	-	-	-	-	-	-	-
Missing	-	-	54	-	[redacted]	[redacted]	-
Prior HCV treatment history							
Naïve	22 (88.0)	27 (90.0)	47 (87.0)	[redacted]	40 (100)	0	127 (87.6)
Experienced	3 (12.0)	3 (10.0)	7 (13.0)	[redacted]	0	47 (100)	18 (12.4)
Type of previous regimen							
IFN-based	-	-	-	-	0	22 (46.8)	12 (8.3)
SOF-based	-	-	-	-	0	25 (53.2)	6 (4.1)
IL28B genotype							
CC	13 (52.0)	10 (33.3)	22 (40.7)	[redacted]	10 (22.7)	20 (50.0)	69 (47.6)
CT	9 (36.0)	18 (60.0)	24 (44.4)	[redacted]	27 (61.4)	18 (45.0)	56 (38.6)
TT	3 (12.0)	2 (6.7)	-	-	-	-	20 (13.8)
Baseline HCV RNA level (IU/mL)							
<6,000,000	9 (36.0)	13 (43.3)	23 (42.6)	[redacted]	36 (90.0)	37 (78.7)	83 (57.2)
≥6,000,000	16 (64.0)	17 (56.7)	31 (57.4)	[redacted]	4 (10.0)	10 (21.3)	62 (42.8)
<10,000,000	12 (48.0)	18 (60.0)	37 (68.5)	[redacted]	39 (97.5)	43 (91.5)	107 (73.8)
≥10,000,000	13 (52.0)	12 (40.0)	17 (31.5)	[redacted]	1 (2.5)	4 (8.5)	38 (26.2)
HCV genotype							
1 (total)	-	-	-	-	-	-	-
1a	-	-	-	-	-	-	-
1b	-	-	-	-	-	-	-

	SURVEYOR-II, Part 1[48, 49, 52, 56]		**SURVEYOR-II, Part 2[23, 49, 53, 55]**		**SURVEYOR-II, Part 3[24, 48, 52]**		**SURVEYOR-II, Part 4[24, 48, 52]**
Baseline characteristics, n (%)	GT2 G/P (300 mg/120 mg) 12 weeks, N=25	GT3 G/P (300 mg/120 mg) 12 weeks, N=30	GT2 G/P 8 weeks, N=54	GT3 G/P 12 or 16 weeks, N=28	TN CC G/P 12 weeks, N=40	TE-PRS CC G/P 16 weeks, N=47	GT2 G/P 8 weeks, N=145[a]
2 (total)	25 (100)	-	54 (100)	-	-	-	145 (100)
3 (total)	-	30 (100)	-	[redacted]	[redacted]	[redacted]	-
4 (total)	-	-	-	-	-	-	-
5 (total)	-	-	-	-	-	-	-
6 (total)	-	-	-	-	-	-	-

Source: CS, Table 18, 19, 20 and 21, pages 79-89.

CC = compensated cirrhosis; DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; SOF = sofosbuvir; HCV = hepatitis C virus; NC = non-cirrhotic; RBV = ribavirin

[a]) Two GT2-infected patients were later determined as GT1 by phylogenetic analysis. These patients were included in the ITT analysis, but were excluded for the comparison to historical threshold.

[b]) At screening, this patient was assessed by the investigator as having cirrhosis but did not end up having qualifying results for cirrhosis per protocol prior to enrolment. The patient did have a historical FibroScan result of 14.0 kPa (F3).

ERG comment

- Although baseline characteristics from the G/P trials are supplied, in most cases baseline characteristics for G/P studies are not reported for the specific population used to compare effectiveness between regimes. It is therefore not possible to ascertain whether the patients in the specific comparisons made are comparable or whether they are representative of those in clinical practice.

4.2.1 Results

The CS reports clinical effectiveness results according to the primary objective (SVR12) for each of the included G/P studies. Here, we will only report results for the studies that had treatment durations that were in line with the anticipated licence indication for the population included in the study and were used in the economic model (see Table 4.3).

In the table below, SVR12 rates for G/P regimens corresponding to the (anticipated) licensed dose and treatment duration are reported. The SVR12 rates from each trial are reported whenever possible from ITT patient subpopulations defined by genotype, treatment history and cirrhosis status.

Table 4.8: Results for relevant G/P studies

Genotype	Subgroup	Study	Regimen	SVR12
GT1	TN NC	ENDURANCE-1[18, 39]	G/P 8 weeks	[redacted]
		SURVEYOR-I, Part 2	G/P 8 weeks	96.6% (28/29)
	TN CC	EXPEDITION-1[47]	G/P 12 weeks	[redacted]
	TE NC	ENDURANCE-1[18, 39]	G/P 8 weeks	[redacted]
		SURVEYOR-I, Part 2	G/P 8 weeks	100% (5/5)
	TE CC	EXPEDITION-1[47]	G/P 12 weeks	[redacted]
GT2	TN NC	SURVEYOR-II, Part 4[24, 48, 52]	G/P 8 weeks	[redacted]
		SURVEYOR-II, Parts 1 and 2[22, 23, 48-50, 52, 56]	G/P 8 weeks	[redacted]
	TN CC	EXPEDITION-1[47]	G/P 12 weeks	[redacted]
	TE NC	SURVEYOR-II, Part 4[24, 48, 52]	G/P 8 weeks	[redacted]
		SURVEYOR-II, Parts 1 and 2[22, 23, 48-50, 52, 56]	G/P 8 weeks	[redacted]
	TE CC	EXPEDITION-1[47]	G/P 12 weeks	[redacted]
GT3	TN NC	ENDURANCE-3[25, 43]	G/P 8 weeks	94.9% (149/157)
	TN CC	SURVEYOR-II, Part 2[22, 23, 48-50, 52, 56]	G/P 12 weeks	100% (24/24)
		SURVEYOR-II, Part 3[24, 52]	G/P 12 weeks	[redacted]
	TE NC	SURVEYOR-II, Part 3[24, 52]	G/P 16 weeks	[redacted]
	TE CC	SURVEYOR-II, Part 2[22, 23, 48-50, 52]	G/P 16 weeks	[redacted]

Genotype	Subgroup	Study	Regimen	SVR12
		SURVEYOR-II, Part 3[24, 52]	G/P 16 weeks:	[redacted]
GT4–6	TN NC	GT4: SURVEYOR-II, Part 4[52]	G/P 8 weeks	[redacted]
		GT5: SURVEYOR-II, Part 4[52]	G/P 8 weeks	[redacted]
		GT6: SURVEYOR-II, Part 4[52]	G/P 8 weeks	[redacted]
	TN CC	GT4: EXPEDITION-1[47]	G/P 12 weeks	[redacted]
		GT5: EXPEDITION-1[47]	G/P 12 weeks	[redacted]
		GT6: EXPEDITION-1[47]	G/P 12 weeks	[redacted]
	TE NC	GT4–6: SURVEYOR-II, Part 4[52]	G/P 8 weeks	[redacted]
	TE CC	GT4–6: EXPEDITION-1[47]	G/P 12 weeks	[redacted]
Source: CS, section B2.7.1, page 108 *ITT population excluding prior SOF+ RBV ± peg-IFN failures				

ERG comment: As can be seen from Table 4.8, numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each group. Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

4.2.2 Health-related quality of life

[redacted]In ENDURANCE-1, '[redacted]' (G/P vs Placebo) and in ENDURANCE-3 '[redacted]' (G/P vs SOF/DCV). [redacted], according to the company.

4.2.3 Subgroup analyses

Subgroup analyses are described in section B2.8 (pages 128-129) of the CS and Appendix E (CS Appendix, pages 385-392). Basic results presented above are already reported by genotype, for people with and without cirrhosis and based on previous treatment (naïve or experienced). Additional subgroups mentioned in the scope are:

- co-infection with HIV
- previous treatment received (with or without DAA-containing regimens)

- people who have received treatment before liver transplantation, and those who have received it after liver transplantation
- response to previous treatment (non-response, partial response, relapsed)
- people who are intolerant to or ineligible for interferon treatment
- people with and without renal impairment

From these subgroups, the company provided results for people co-infected with HIV (ENDURANCE-1 - GT1/NC/TN+TE). No results are provided for any of the other subgroups that were used in the economic model.

4.2.4 Adverse events

The summary of the safety profile for G/P in the SmPC[11] shows that in patients treated for eight, 12 or 16 weeks with compensated liver disease (with or without cirrhosis), based on Phase 2 and 3 studies which evaluated approximately 2,300 patients, the most commonly reported adverse reactions (incidence ≥ 10%) were headache and fatigue. Less than 0.1% of patients treated with G/P had serious adverse reactions (transient ischaemic attack). The proportion of patients treated with G/P who permanently discontinued treatment due to adverse reactions was 0.1%. The type and severity of adverse reactions in patients with cirrhosis were overall comparable to those seen in patients without cirrhosis.[11]

The most commonly reported adverse reactions identified in patients treated with G/P are reported in Table 4.9. The adverse reactions are listed below by body system organ class and frequency.

Table 4.9: Adverse reactions identified with G/P

Frequency	Adverse reactions
Nervous system disorders	
Very common	headache
Gastrointestinal disorders	
Common	diarrhoea, nausea
General disorders and administration site conditions	
Very common	fatigue
Common	asthenia
Source: Glecaprevir & Pibrentasvir (Maviret) Draft SPC_26-06-2017[11] Very common: ≥ 1/10), common: ≥ 1/100 to < 1/10)	

Adverse events (AEs) in the CS are reported in four groups. First, AEs from a placebo-controlled study (ENDURANCE-2); second, AEs from an active-controlled study (ENDURANCE-3); third, AEs from all randomised patients from 21 arms of the Phase II/III studies who received at least one dose of G/P 300 mg/120 mg OD without RBV; and fourth, AEs from a study including patients with chronic kidney disease (CKD Stage 4/5; EXPEDITION-4).

Placebo-controlled study: ENDURANCE-2

In the placebo-controlled analysis set, 302 (202 G/P, 100 placebo) patients received at least one dose of study drug in ENDURANCE-2. Patients were genotype GT2, NC, TN or TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN. Treatment was 12 weeks of G/P at a dose of 300 mg/120 mg. Adverse events from ENDURANCE-2 are reported in Table 4.10.

Table 4.10: ENDURANCE-2 and ENDURANCE-3 adverse events summaries

Adverse events, n (%)	ENDURANCE-2		ENDURANCE-3	
	G/P (300 mg/ 120 mg), 12 weeks (N=202)	Placebo 12 weeks (N=100)	G/P (300 mg/ 120 mg) 12 weeks (N=233)	SOF + DCV 12 weeks (N=115)
≥1 AE	131 (64.9)	58 (58.0)	177 (76.0)	80 (69.6)
≥1 treatment-related AE	[redacted]	[redacted]	112 (48.1)	50 (43.5)
Grade 3 or 4 AE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3/4 AEs				
Alanine aminotransferase increased	[redacted]	[redacted]	NR	NR
Ankle fracture	[redacted]	[redacted]	NR	NR
Aspartate aminotransferase increased[a]	[redacted]	[redacted]	NR	NR
Bile duct stone[c]	[redacted]	[redacted]	NR	NR
Gamma-glutamyltransferase increased[a]	[redacted]	[redacted]	NR	NR
Haemorrhoids	[redacted]	[redacted]	NR	NR
Joint dislocation[b]	[redacted]	[redacted]	NR	NR
Pulmonary pain	[redacted]	[redacted]	NR	NR
Neutropaenia	[redacted]	[redacted]	NR	NR
≥1 treatment-related SAE	NR	NR	NR	NR
Deaths	NR	NR	NR	NR
Discontinuation due to AEs	NR	NR	1	NR
Common AEs[†]				
Headache	24 (11.9)	12 (12.0)	60 (25.8)	23 (20.0)
Fatigue	23 (11.4)	10 (10.0)	44 (18.9)	16 (13.9)
Insomnia	NR	NR	NR	NR
Nausea	[redacted]	[redacted]	32 (13.7)	15 (13.0)
Oropharingeal pain	[redacted]	[redacted]	NR	NR
Nasopharyngitis	NR	NR	[redacted]	[redacted]
Upper respiratory infection	NR	NR	[redacted]	[redacted]
Irritability	NR	NR	NR	NR
Cough	NR	NR	NR	NR
Pruritus	[redacted]	[redacted]	NR	NR
Dyspepsia	NR	NR	NR	NR
Back pain	NR	NR	NR	NR
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	NR	NR
Constipation	NR	NR	NR	NR

Adverse events, n (%)	ENDURANCE-2		ENDURANCE-3	
	G/P (300 mg/ 120 mg), 12 weeks (N=202)	Placebo 12 weeks (N=100)	G/P (300 mg/ 120 mg) 12 weeks (N=233)	SOF + DCV 12 weeks (N=115)
Arthralgia	NR	NR	NR	NR
Dyspnoea	NR	NR	NR	NR
Abdominal pain	NR	NR	NR	NR
Muscle spasms	NR	NR	NR	NR
Rash	NR	NR	NR	NR
Anxiety	NR	NR	NR	NR
Vomiting	NR	NR	NR	NR
Dry skin	NR	NR	NR	NR
Anaemia	NR	NR	NR	NR
Myalgia	NR	NR	NR	NR
Sleep disorder	NR	NR	NR	NR
Dyspnoea exertional	NR	NR	NR	NR
Decreased appetite	NR	NR	NR	NR
Disturbance in attention	NR	NR	NR	NR
Pyrexia	NR	NR	NR	NR
Source: CS, Tables 197 and 199, pages 158-159. AE = adverse event †Common AEs were those that occurred in ≥5% of patients in any treatment group.				

The risk difference (G/P versus placebo) [redacted]

[redacted] G/P patients ([redacted]%) experienced [redacted] ([redacted]%) AEs of Grade ≥3 in severity compared to [redacted] ([redacted]%) for placebo patients.

Active-controlled study: ENDURANCE-3

In the active-controlled analysis set, 233 patients were randomised and received G/P 300 mg/120 mg for 12 weeks and 115 patients received SOF + DCV (2:1 randomisation ratio) in ENDURANCE-3 (GT3-infected patients without cirrhosis). Adverse events from ENDURANCE-3 are reported in Table 4.10.

[redacted]

Uncontrolled Phase II/III studies

The Phase II and III analysis set, included 2,265 patients who received at least one dose of co-administered or co-formulated G/P 300 mg/120 mg OD (any duration) without RBV (see Table 4.11).

Table 4.11: AEs reported for ≥5.0% of patients (Phase II and III analysis set)

Preferred term	Phase II and III analysis set, (N=2265), n (%)	
	All AEs	Study drug-related AEs[a]
Any AE	1,529 (67.5)	[redacted]
Headache	410 (18.1)	[redacted]
Fatigue	330 (14.6)	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]

[a]Investigator assessment; AE = adverse event

[redacted] ([redacted]) of patients with AEs experienced AEs that were Grade ≥3 (severe) in maximum severity. Of the [redacted] patients who experienced an AE of Grade ≥3 severity, [redacted] patients had AEs considered study drug-related ([redacted] patient each with [redacted]; and [redacted] patient with [redacted]).

Seven deaths were reported in the Phase II and III analysis set (N = [redacted]). [redacted].

Patients with chronic kidney disease: EXPEDITION-4

EXPEDITION-4 is a single arm study, including TN patients of all genotypes and TE-PRS for GT1, GT2, GT4, GT5 and GT6; patients were NC or CC and had severe renal impairment or end-stage renal disease (including those on dialysis). Treatment duration was 12 weeks. The aim of the study was to evaluate the efficacy of 12-week treatment with G/P in TN or TE-PRS NC and CC patients with or without stage 4 or 5 CKD, as measured by the proportion of patients with SVR12 and to evaluate the safety and tolerability of the treatment regimen. Patients were recruited from 28 study locations in the United States, Australia, Belgium, Canada, France, Greece, Italy and New Zealand, and two sites (seven patients) in the United Kingdom.

Patients enrolled in EXPEDITION-4 had CKD Stage 4/5, and the majority were on dialysis. Given the severity of the underlying renal disease and its associated comorbidities, the frequency and severity of the AEs in patients enrolled in this study were expected to be higher than in patients enrolled in the other registrational studies. Therefore, adverse events in this study are reported separately.

[redacted] (see Table 4.12).

Table 4.12: Overview of AEs (EXPEDITION-4)

	EXPEDITION-4, n (%) (N=104)
Any AE	74 (71.2)
Any DAA-related AE[a,b]	[redacted]
An AE Grade ≥3	[redacted]
Any DAA-related AE Grade ≥3[a,b]	[redacted]
Any SAE	25 (24.0)
Any DAA-related SAE[a,b]	0
Discontinuation of study drug due to:	
Any AE	4 (3.8)
Any DAA-related AE[a,b]	[redacted]
Any fatal AE	[redacted]
All deaths[c]	1 (1.0)

Source: CS Appendix F, Table 206, page 165
[a]DAAs = GLE, PIB, or G/P; [b]Investigator assessment; [c]Includes nontreatment-emergent deaths
AE = adverse event; DAA = direct-acting antiviral agent; G/P = glecaprevir/pibrentasvir; GLE = glecaprevir; PIB = pibrentasvir; SAE = serious adverse event

Among patients in EXPEDITION-4, the most frequently reported (≥10.0% of patients) AEs were pruritus, fatigue, and nausea (see Table 4.13).

Table 4.13: Treatment-emergent adverse events reported in ≥ 5.0% of patients

MedDRA 19.0 Preferred Term	EXPEDITION-4, (N = 104), n (%)
Any adverse event	[redacted]
Pruritus	[redacted]
Fatigue	[redacted]
Nausea	[redacted]
Asthenia	[redacted]
Diarrhoea	[redacted]
Decreased appetite	[redacted]
Headache	[redacted]
Vomiting	[redacted]
Dizziness	[redacted]
Dyspnoea	[redacted]

Source: CSR, Table 25, page 138[59]
EXPEDITION-4: G/P, 300 mg/120 mg QD for 12 weeks
MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily

Of the patients in EXPEDITION-4 experiencing DAA-related events (N=[redacted]), [redacted] ([redacted]%) had events of maximum severity of Grade 1 (mild), [redacted] ([redacted]%) had a maximum severity of Grade 2, and [redacted] ([redacted]%) had a maximum severity of Grade 3.

[redacted]

[redacted]

[redacted] (See Table 4.14). [redacted] In the subset of patients who were not receiving dialysis (N=[redacted]), [redacted] patients had Grade 3 or 4 creatinine values and [redacted] patients had Grade 3 or 4 creatinine clearance values. [redacted].

Table 4.14: Number (%) of patients with CTCAE Grade 3/4 laboratory values increasing in grade from baseline during the treatment period (EXPEDITION-4)

Variable (criterion)	EXPEDITION-4, (N=104), n/N* (%)
Haemoglobin (<80 g/L)	5/104 (4.8)
Platelet count (<50 × 10^9/L)	[redacted]
Leukocytes (<2.0–1.0 × 10^9/L)	[redacted]
Total neutrophils (<1 × 10^9/L)	[redacted]
INR (>2.5 × ULN)	[redacted]
ALT (>5 × ULN)	[redacted]
AST (>5 × ULN)	[redacted]
GGT (>5 × ULN)	[redacted]
Alkaline phosphatase (>5 × ULN)	[redacted]
Total bilirubin (>3 × ULN)	[redacted]
Creatinine clearance, calculated (<30 mL/min)	[redacted]
Albumin (<20 g/L)	[redacted]
Cholesterol (>10.34 mmol/L)	[redacted]
Glucose (>13.9 mmol/L)	[redacted]
Creatinine (>3 × ULN)	[redacted]
Sodium (<130 mmol/L)	[redacted]
Potassium (>6.0 mmol/L)	[redacted]
Triglycerides (>5.7 mmol/L)	[redacted]

Source: CS Appendix F, Table 207, page 166

Note: n/N* indicates the number of patients with postbaseline values for the respective parameter meeting the criteria; grade must have been more extreme than baseline; Of note, no patients in EXPEDITION-4 met criteria for potential hepatotoxicity based on results for a single laboratory parameter (ALT or total bilirubin) or based on results for both ALT and total bilirubin. ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GGT = gamma-glutamyl transferase; INR = international normalized ratio; ULN = upper limit of normal.

[redacted] patients experienced an i[redacted] in the EXPEDITION-4 study. [redacted]

[redacted]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As described in section 4.2.1 of this report, 81 publications (reporting on 79 studies) were identified as meeting the eligibility criteria. Fourteen of these publications, representing seven studies, involved G/P. Therefore, the remaining 67 publications, representing 72 studies, involved comparators.

Most of these comparator studies are not mentioned in the clinical effectiveness section of the CS. Only a few are briefly mentioned in section B.2.10 of the CS to explain that it is not feasible to form any network between G/P and any relevant comparator therapies.

The only place these studies are mentioned is in Tables 63 to 78, describing the sources for inputs in the economic model. No further details of the comparator studies are reported in the main CS. In Appendix D, the company presents an overview of comparator studies (see CS, Appendix D, Table 123, page 17-34 and Table 4.15 below). Baseline characteristics for the comparator studies are presented in Table 124 (CS, Appendix D, page 34). However, because results used in the economic model are mostly from subgroups of patients in these studies (based on genotype, treatment experience and cirrhosis status), baseline characteristics for the total population of each study cannot be used to assess whether populations are comparable to those from G/P studies. In most cases baseline characteristics for G/P studies are not reported for the specific population used for effectiveness data. Therefore, the ERG was unable to assess differences in patient populations between G/P studies and comparator studies.

A list of SVR rates for comparators used in the economic model are presented in Tables 65 and 66 of the CS (CS, pages 158-163). We have summarised these two tables in Table 4.16 below, and we have added SVR rates from G/P studies in the relevant populations.

Table 4.15: Overview of studies of comparator DAAs identified by the SLR

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Reference(s)
OBV/PTV/RTV + DSV						
1	GARNET	Single-arm, open-label study	Patients with CHC GT1b whose treatment status was not reported and were NC	OBV/PTV/RTV + DSV		Welzel 2017[71]
2	Arama et al (2017)	Cohort study (limited details in abstract)	Patients with CHC GT1 whose treatment status was not reported and who had CC	OBV/PTV/RTV + DSV and RBV		Arama 2017[72]
3	AGATE-I	Randomised, open-label trial	Patients with CHC GT4 whose treatment status was not reported and had CC	OBV (25 mg)/PTV (150 mg)/RTV (100 mg) once daily with weight-based RBV for 12 (Arm A) or 16 weeks (Arm B)		Asselah 2016[73]
4	PEARL-I	Randomised, open-label study	Patients with CHC GT1b/4 who were treatment-naïve and TE and were NC or had CC	OBV (25 mg)/PTV (150 mg)/RTV (100 mg) once daily for 12 or 24 weeks OBV (25 mg)/PTV (150 mg)/RTV (100 mg) once daily and weight-based RBV for 12 weeks		Hézode 2015b[74]
5	PEARL-II	Randomised, open-label study	Patients with CHC GT1b who were TE and NC	OBV/PTV/RTV + DSV	OBV/PTV/RTV + DSV + RBV	Andreone 2014[75]
6	PEARL-III	Randomised, double blind study	Patients with CHC GT1b who were TN and NC	OBV/PTV/RTV + DSV + RBV	OBV/PTV/RTV + DSV + Placebo RBV	Ferenci 2014[76]
7	PEARL-IV	Randomised, double blind study	Patients with CHC GT1a who were TN and NC	OBV/PTV/RTV + DSV + RBV	OBV/PTV/RTV + DSV +Placebo RBV	Ferenci 2014[76]
8	TURQUOISE-II	Randomised, open-label study	Patients with CHC GT1 whose TN or TE status was not reported and had CC	OBV/PTV/RTV + DSV+ RBV for 12 weeks	OBV/PTV/RTV + DSV + RBV for 24 weeks	Poordad 2014[77]

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Reference(s)
9	TURQUOISE-III	Single-arm, open-label study	Patients with CHC GT1b who were TN and TE and had CC	OBV/PTV/RTV + DSV for 12 weeks		Feld 2016[78]
10	Navigator	Non-randomised, open-label study	Patients with CHC GT1/2/3 who were TN and NC	OBV/PTV/RTV + RBV in GT1-3 OBV/PTV/RTV in GT1-3		Lawitz 2015c[79]
11	SAPPHIRE-I	Randomised, double blind study	Patients with CHC GT1 who were TN and NC	OBV/PTV/RTV + DSV + RBV	Placebo followed by OBV/PTV/RTV + DSV + RBV	Feld 2014[80]
12	SAPPHIRE-II	Randomised, double blind study	Patients with CHC GT1 who were TE and NC	OBV/PTV/RTV + DSV + RBV	Placebo followed by OBV/PTV/RTV + DSV + RBV	Zeuzem 2014b[81]
13	Kowdley (2014)	Randomised, open-label study	Patients with CHC GT1 who were treatment-naïve and TE and NC	OBV (25mg)/PTV (100/150/200 mg)/RTV (100 mg) once daily +/- DSV (400 mg) twice daily +/- RBV dosed by weight, twice daily for 8, 12 or 24 weeks		Kowdley 2014b[82]
14	MALACHITE I	Randomised, open-label study	Patients with CHC GT1 who were TN and NC	OBV/PTV/RTV + DSV + RBV in GT1a and GT1b OBV/PTV/RTV + DSV in GT1b	TVR + IFN + RBV in GT1a and GT1b.	Dore 2016[83]
15	MALACHITE II	Randomised, open-label study	Patients with CHC GT1 who were TE and were NC	OBV (25mg)/PTV (150 mg)/RTV (100 mg) once daily + DSV (250 mg) twice daily plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks	TVR co-administered with IFN and weight-based RBV for 12 weeks, followed by IFN and weight-based RBV for either 12 or 36 weeks, per local prescribing information.	Dore 2016[83]
EBR/GZR						

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Reference(s)
16	MK-5172-035/C-WORTHY	Randomised, double blind study	Patients with CHC GT1 who were TN and TE, with or without cirrhosis	EBR (20/50 mg)/GZR (100 mg) +/- RBV for 8, 12 or 18 weeks		Lawitz 2015b[84]
17	C-EDGE TE	Randomised, open-label study	Patients with CHC GT1/4/6 who were TE and were with or without cirrhosis	EBR/GZR for 12 weeks EBR/GZR + RBV for 12 or 16 weeks		Kwo 2017[85]
18	MK-5172-077	Randomised, open-label study	Patients with CHC GT1/4 who were TN and TE and were with or without cirrhosis	EBR/GZR for 12 weeks	SOF + IFN + RBV for 12 weeks	Sperl 2016[86]
19	C-ISLE (no trial ID)	Randomised, open-label study	Patients with CHC GT3 who were TN and TE	EBR/GZR + SOF ± RBV for 8 or 12 weeks (five arms)		Foster 2017[87]
20	C-EDGE TN	Phase II, randomised clinical trial	Patients with CHC GT1/4/6 who were TN	EBR (50 mg)/GZR (100 mg) FDC	Placebo for 12 weeks, followed by the intervention	Zeuzem 2015[88]
SOF/LDV						
21	Gane (2015)	Phase II, randomised, open-label study	Patients with CHC GT1/2/3/6 who were TN and TE, with or without cirrhosis	SOF/LDV +/- RBV for 12 or 24 weeks SOF + IFN + RBV for 12 weeks SOF/VEL (25/100mg) +/- RBV for 8 weeks		Gane 2015[89]
22	ELECTRON	Randomised, open-label study	Patients with CHC GT2/3 who were TN and whose cirrhosis status was not reported	SOF + RBV for 8 or 12 weeks SOF + RBV for 12 weeks + IFN for 4 or 8 weeks SOF + IFN + RBV for 8 or 12 weeks SOF for 12 weeks SOF/LDV +/- RBV for 6 or 12 weeks		Gane 2014[90]

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Reference(s)
23	ION-1	Randomised, open-label study	Patients with CHC GT1 who were TN and were with or without cirrhosis	SOF/LDV for 12 weeks SOF/LDV for 24 weeks	SOF/LDV + RBV for 24 weeks SOF/LDV + RBV for 12 weeks	Afdhal 2014b[91]
24	ION-2	Randomised, open-label study	Patients with CHC GT1 who were TE and were with or without cirrhosis	SOF/LDV for 12 weeks SOF/LDV for 24 weeks	SOF/LDV + RBV for 12 weeks SOF/LDV + RBV for 24 weeks	Afdhal 2014a[92]
25	ION-3	Randomised, open-label study	Patients with CHC GT1 who were TN and NC	SOF/LDV +/- RBV for 8 weeks	SOF/LDV for 12 weeks	Kowdley 2014a[93]
26	Study 1119	Phase II, non-randomised, open-label study	Patients with CHC GT4/5 who were treatment-naïve and TE and were with or without cirrhosis	SOF/LDV for up to 12 weeks in GT4 and GT5		Abergel 2016[94]
27	SIRIUS	Randomised, double blind study	Patients with CHC GT1 who were TE and were cirrhotics only	SOF/LDV	SOF/LDV + RBV	Bourlière 2015[95]
28	Kohli (2015)	Phase II, non-randomised, open-label study	Patients with CHC GT1/4 who were TN and TE and were with or without cirrhosis	SOF/LDV for 12 weeks SOF/LDV/GS-9669 for 4, 6 or 12 weeks	N/A	Kohli 2015[96]
SOF/VEL						
21	Gane (2015) –	see details above				
29	ASTRAL-1	Randomised, double blind study	Patients with CHC GT1/2/4/5/6 who were TN and TE and were with or without cirrhosis	SOF/VEL for 12 weeks	Placebo	Feld 2015[97]
30	ASTRAL-2	Randomised, open-label study	Patients with CHC GT2 who were TN and TE and	SOF/VEL fixed dose combination for 12 weeks	SOF + RBV for 12 weeks	Foster 2015b[98]

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Reference(s)
			were with or without cirrhosis			
31	ASTRAL-3	Randomised, open-label study	Patients with CHC GT3 who were TN and TE and were with or without cirrhosis	SOF/VEL 12 weeks	SOF + RBV for 24 weeks	Foster 2015b[98]
32	ASTRAL-4	Randomised, open-label study	Patients with CHC GT1/2/3/4/5/6 who were TN and TE and had DCC	SOF/VEL for 12 weeks SOF/VEL + RBV for 12 weeks	SOF/VEL for 24 weeks	Curry 2015[99]
33	Pianko (2015)	Phase II, randomised, open-label study	Patients with CHC GT1/3 who were TE and were with or without cirrhosis	SOF/VEL (25/100mg) +/- RBV	N/A	Pianko 2015[100]
34	Everson (2015)	Phase II, randomised, open-label study	Patients with CHC GT1/2/3/4/5/6 who were TN and NC	SOF/VEL (25/100 mg) +/- RBV for 8 or 12 weeks	N/A	Everson 2015[101]
SOF						
22	ELECTRON -	see details above				
30	ASTRAL-2 -	see details above				
31	ASTRAL-3 -	see details above				
35	Wehmeyer (2015)	Prospective study (open or blind not reported)	Patients with CHC GT4 who were TN and TE and were NC or CC	SOF + IFN + RBV IFN + RBV		Wehmeyer 2015[102]
36	BOSON	Randomised, open-label study	Patients with CHC GT2/3 who were TN and TE and had CC	SOF + RBV for 16 weeks SOF + RBV for 24 weeks SOF + IFN + RBV for 12 weeks		Foster 2015a[103]
37	Lawitz (2015)	Non-randomised, open-label study	Patients with CHC GT2/3 who were TE and were cirrhotics only	SOF + IFN + RBV for 12 weeks	N/A	Lawitz 2015a[104]

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Reference(s)
38	ATOMIC	Randomised, open-label study	Patients with CHC GT1/4/5/6 who were TN and had no history of any other clinically significant chronic liver disease	SOF + IFN + RBV for 12 weeks SOF + IFN + RBV for 24 weeks	SOF + IFN + RBV for 12 weeks	Lawitz 2014a[105]
39	Rodriguez-Torres (2013)	Phase II, randomised, double blind study	Patients with CHC GT1 who were TN and cirrhosis status was not reported	SOF (100 mg) + IFN + RBV SOF (200 mg) + IFN + RBV SOF (400 mg) + IFN + RBV	Placebo + IFN + RBV	Rodriguez-Torres 2013[106]
40	VALENCE	Randomised, double blind study	Patients with CHC GT2/3 who were treatment-naïve and TE and were with or without cirrhosis	SOF for 12 weeks in GT2/3 SOF for 24 weeks in GT3	N/A	Zeuzem 2014a[107]
41	FUSION	Randomised, double blind study	Patients with CHC GT3 who were TE and were with or without cirrhosis	SOF + RBV for 16 weeks	SOF + RBV for 12 weeks followed by placebo for 4 weeks	Jacobson 2013[108]
42	POSITRON	Randomised, double blind study	Patients with CHC GT2/3 who were IFN intolerant or ineligible and were with or without cirrhosis	SOF + RBV for 12 weeks	Placebo	Jacobson 2013[108]
43	NEUTRINO	Single-arm, open-label study	Patients with CHC GT1/4/5/6 who were TN and were with or without cirrhosis	SOF + IFN + RBV	N/A	Lawitz 2013a[109]
44	FISSION	Randomised, open-label study	Patients with CHC GT2/3 who were TN and had no hepatic decompensation	SOF + RBV for 12 weeks	IFN + RBV for 24 weeks.	Lawitz 2013a[109]
45	PROTON	Randomised, double blind study	Patients with CHC GT1/2/3 who were TN and were NC	SOF (200 mg) in GT1 SOF (400 mg) in GT1 SOF (400 mg) in GT2/3	Placebo (GT 1). Participants with GT 1 HCV infection were	Lawitz 2013b[110]

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Reference(s)
					randomised to receive placebo to match SOF (4 tablets) + IFN + RBV for 12 weeks followed by IFN + RBV for up to an additional 36 weeks.	
SOF/DCV*						
46	ALLY- 3+	Randomised, open-label study	Patients with CHC GT3 who were TN and TE and had advanced fibrosis or CC	1: SOF/DCV + RBV for 12 weeks	2: SOF/DCV + RBV for 16 weeks	Leroy 2016[111]
47	ALLY3	Non-randomised, open-label study	Patients with CHC GT3 who were TN and TE and had no decompensated liver disease	A1: SOF/DCV in TN	A2: SOF/DCV in TE	Nelson 2015[112]
48	Hézode (2017b)	Single-arm, open-label study	Patients with CHC GT 3 who were TN	SOF/DCV for 8 weeks		Hézode 2017b[113]
49	AI444040	Randomised, open-label study	Patients with CHC GT1/2/3 who were TN and were NC	SOF/DCV +/- RBV		Sulkowski 2014[114]
SMV/SOF						
50	PLUTO	Single-arm, open-label study	Patients with CHC GT4 who were TN and TE and were NC or CC	SMV (150 mg)/SOF (400 mg)		Buti 2017[115]
51	SMV-SOF	Randomised, open-label study		SMV/SOF	IFNα-2b + RBV + SOF for 12 weeks	Pearlman 2015[116]
52	OPTIMIST 2	Single-arm, open-label study	Patients with CHC GT1 who were TN and TE and had cirrhosis only	SMV/SOF		Lawitz 2016[117]

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Reference(s)
53	COSMOS	Randomised, open-label study	Patients with CHC GT1 who were TN and NR and had no hepatic decompensation	SMV/SOF for 24 weeks SMV/SOF for 12 weeks	SMV/SOF+ RBV for 12 or 24 weeks	Lawitz 2014b[118]
DCV						
54	Pol (2012)	Phase II, randomised, double blind study	Patients with CHC GT1 who were TN and were NC	A: DCV + IFNα-2a + RBV B: DCV + IFNα-2a + RBV C: DCV + IFNα-2a + RBV	Placebo, IFNα-2a, RBV (D) Interventions: Drug: Placebo Drug: IFNα-2a Drug: RBV	Pol 2012[119]
55	Rodriguez-Torres (2016)	Phase III, single-arm open-label study	Patients with CHC GT1 who were TN, compensated cirrhotics were capped at approximately 25%	DCV + IFN + RBV	N/A	Rodriguez-Torres 2016[120]
56	COMMAND-1	Randomised, double blind study	Patients with CHC GT1/4 who were TN and were NC	DCV+IFNα-2a + RBV (20 mg) DCV+IFNα-2a + RBV (60 mg)	Placebo+IFNα-2a+ RBV	Hézode 2015a[121]
57	COMMAND-4	Randomised, double blind study	Patients with CHC GT1 who were TN and were NC	DCV + IFNα-2a + RBV	Placebo Comparator: Placebo matching DCV + IFNα-2a + RBV	Hézode 2015c[122]
58	A1444-031	Randomised, double blind study	Patients with CHC GT2/3 who were TN and had no DC	DCV + IFNα-2a + RBV for 12 weeks DCV + IFNα-2a + RBV for 12 weeks	Control Placebo + IFNα-2a + RBV	Dore 2015[123]
SMV/DCV						
59	LEAGUE-1	Randomised, open-label study	Patients with CHC GT1 who were TN and TE, patients with CC were permitted	SMV/DCV +/- RBV		Zeuzem 2016[124]

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Reference(s)
60	Hézode et al (2017a)	Single-arm, open-label study	Patients with CHC GT1b who were TN and were NC or CC	SMV/DCV for 12 or 24 weeks		Hézode 2017a[125]
GZR						
61	MK-5172-038	Randomised, double blind study	Patients with CHC GT1 who were TN and were NC	GZR (25 mg) + IFN + RBV GZR (50 mg) + IFN + RBV GZR (100 mg) + IFN + RBV	N/A	Lagging 2016[126]
62	MK-5172-003 or Manns (2014)	Randomised, double blind study	Patients with CHC GT1 who were TN CC patients were allowed	GZR (100/200/400/800 mg) + IFN + RBV for 12 weeks followed by 12 or 36 weeks of IFN RBV, based on response guided therapy As the result of an interim analysis, participants assigned to the GZR (400/800 mg) group were unblinded and transitioned to GZR (100 mg) once daily + IFN + RBV	BOC (800 mg) in TN NC participants start a 4 week lead-in with IFN + RBV, then receive BOC (800 mg) + IFN + RBV for 24 weeks followed by 0 or 20 weeks of IFN + RBV, based on response guided therapy.	Manns 2014a[127]
PTV/RTV+DSV						
63	Poordad (2013)	Phase II, non-randomised, open-label study	Patients with CHC GT1 who were TN and NR, and NC	PTV (150/250 mg)/RTV (100 mg) + DSV + RBV		Poordad 2013[128]
SMV						
64	QUEST-1	Randomised, double blind study	Patients with CHC GT1 who were TN and had no hepatic decompensation	SMV (150 mg) once daily for 12 weeks + IFN + RBV for 24 or 48 weeks	IFN + RBV + Placebo for 48 weeks	Jacobson 2014[129]
65	QUEST-2	Randomised, double blind study	Patients with CHC GT1 who were TN and had no hepatic decompensation	SMV (150 mg) once daily for 12 weeks + IFN + RBV for 24 or 48 weeks	IFN + RBV + Placebo for 48 weeks	Manns 2014b[130]
66	RESTORE	Single-arm, open-label study	Patients with CHC GT4 who were TN and TE and	SMV	N/A	Moreno 2015[131]

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Reference(s)
			had no hepatic decompensation			
67	PILLAR	Randomised, double blind study	Patients with CHC GT1 who were TN and NC	SMV (75/150 mg) for 12 or 24 weeks + IFN + RBV 24/48		Fried 2013[132]
68	OPERA-1	Randomised, double blind study	Patients with CHC GT1 who were TN and TE, and NC	SMV (25/75/150/200 mg)		Manns 2011[133]
69	ASPIRE	Randomised, double blind study	Patients with CHC GT1 who were TE, cirrhosis status was not reported	SMV (100/150 mg) for 12, 24 or 48 weeks + IFN + RBV for 48 weeks		Zeuzem 2014c[134]
70	PROMISE	Randomised, double blind study	Patients with CHC GT1 who were TE and had no hepatic decompensation	SMV (150 mg) once daily for 12 weeks + IFN + RBV for 24 or 48 weeks	IFN + RBV + Placebo for 48 weeks	Forns 2014[135]
ASV/DCV						
71	Hallmark QUAD	Single-arm, open-label study	Patients with CHC GT1 who were TE, patients with CC were permitted	ASV/DCV + IFNα-2a + RBV for 24 weeks	N/A	Jensen 2015[136]
72	Everson (2014)	Randomised, open-label study	Patients with CHC GT1/4 who were TN and NC	ASV (200 mg)/DCV (30/60 mg) + BMS-791325 (75/150mg) +/- RBV		Everson 2014[137]

Source: CS Appendix D, Table 123, page 16.

ASV = asunaprevir; CC = compensated cirrhosis; DCV = daclatasvir; DSV = dasabuvir; EBR = elbasvir; FDC = fixed dose comparison; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; NC = non-cirrhotic; NR = non-responder = OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SC = subcutaneously; SMV = simeprevir = SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naïve; TVR = telaprevir; VEL = velpatasvir

Table 4.16: SVR12 rates for all included treatments

Geno -type	Treatment (duration in weeks)			
	TN		TE	
	NC	CC	NC	CC
1	• G/P (8): [redacted] • SOF/VEL (12): 98.4% (251/255)[e] • EBR/GZR[a] (12[d]): 93.2%[c] • SOF/LDV (8): F0–F1: 95.2% (80/84); F2–F3: 94.4% (68/72) • OBV/PTV/RTV + DSV ± RBV(12): [redacted][c] • Best supportive care (watchful waiting): 0%*	• G/P (12): [redacted] • SOF/VEL (12): 98.6% (72/73)[e] • EBR/GZR[a] (12[d]): 95.9%[c] • SOF/LDV (12): 94.1% (32/34) • OBV/PTV/RTV + DSV ± RBV (12/24): 96.4%[c] • Best supportive care (watchful waiting); 0%*	• G/P (8): [redacted] • SOF/VEL (12): 98.4% (251/255)[e] • EBR/GZR[a] (12): 93.4%[c] • SOF/LDV (12): 95.4% (83/87) • OBV/PTV/RTV + DSV ± RBV (12): 97.4%[c,i] • Best supportive care (watchful waiting): 0%*	• G/P (12): [redacted] • SOF/VEL (12): 98.6% (72/73)[e] • EBR/GZR[a] (12): 93.2%[c] • SOF/LDV (12): 86.4% (19/22) • OBV/PTV/RTV + DSV ± RBV (12/24): 98.5%[c,i] • Best supportive care (watchful waiting): 0%*
2	• G/P (8): [redacted] **Comparators for IFN-eligible patients:** • Peg-IFN + RBV (24): 81.5% (44/54) • Best supportive care (watchful waiting): 0%* **Comparators for IFN-ineligible patients:** • SOF/VEL (12): 99.0% (99/100)[e] • SOF + RBV (12): 96.3% (180/187) • Best supportive care (watchful waiting): 0%*	• G/P (12): [redacted] **Comparators for IFN-eligible patients:** • SOF/VEL (12): 100.0% (15/15)[e] • Best supportive care (watchful waiting): 0%* **Comparators for IFN-ineligible patients:** • SOF/VEL (12): 100.0% (15/15)[e] • SOF + RBV (12): 89.7% (26/29) • Best supportive care (watchful waiting): 0%*	• G/P (8): [redacted] • SOF/VEL (12): 100.0% (15/15)[e] • SOF + RBV (12): 88.5% (69/78) • Best supportive care (watchful waiting): 0%*	• G/P (12): [redacted] • SOF/VEL (12): 100.0% (4/4)[e] • SOF + RBV (12): 77.3% • Best supportive care (watchful waiting): 0%*
3	• G/P (8): 94.9% (149/157) • SOF/VEL (12): 98.2% (160/163) • SOF + DCV (12): 96.8% (184/190)	• G/P (12): [redacted] • SOF/VEL (12): 96.7% (116/120) • SOF + DCV + RBV (24): 100% (5/5)	• G/P (8): 95.5% (21/22) • SOF/VEL (12): 91.2% (31/34) • SOF + DCV (12): 94.1% (32/34)	• G/P (12): [redacted] • SOF/VEL (12): 89.9% (62/69) • SOF + DCV + RBV (24): 100% (5/5)[k]

Geno -type	Treatment (duration in weeks)			
	TN		TE	
	NC	CC	NC	CC
	• Best supportive care (watchful waiting): 0%*	• SOF + peg-IFN + RBV (12): 91.3% (21/23) • SOF + RBV (24): 77.6% (45/58) • Best supportive care (watchful waiting): 0%*	• SOF + peg-IFN + RBV (12); NR • Best supportive care (watchful waiting): 0%*	• SOF + peg-IFN + RBV (12): 85.7% (30/35) • SOF + RBV (24): 59.0% (49/83) • Best supportive care (watchful waiting): 0%*
4	• G/P (8): [redacted] • SOF/VEL (12): 100.0% (89/89)[e] • EBR/GZR[a] (12[d]): 100.0% (16.71/16.71)[g] • OBV/PTV/RTV + RBV (12): 100.0% (42/42)[c, f] • Best supportive care (watchful waiting): 0%*	• G/P (12): [redacted] • SOF/VEL (12): 100.0% (27/27)[e] • EBR/GZR[a] (12[d]): 100.0 (1.29/1.29)[g] • SOF/LDV (12): 100.0% (1/1) • OBV/PTV/RTV + RBV (12)[b]: 96.7% (29/30)[c] • Best supportive care (watchful waiting): 0%*	• G/P (8): [redacted][l] • SOF/VEL (12): 100.0% (89/89)[e] • EBR/GZR[a] (12) 100.0% (3/3)[g] • SOF/LDV (12): 84.6% (11/13) • OBV/PTV/RTV + RBV (12): 100.0% (49/49)[c, i] • Best supportive care (watchful waiting): 0%*	• G/P (12): [redacted][l] • SOF/VEL (12): 100.0% (27/27)[e] • EBR/GZR[a] (12) 66.7% (4/6)[g] • SOF/LDV (12): 100.0% (9/9) • OBV/PTV/RTV + RBV (12): 98.2% (N=29)[c, i, m] • Best supportive care (watchful waiting): 0%*
5	• G/P (8): [redacted] • SOF/VEL (12): 96.6% (28/29)[e] • Best supportive care (watchful waiting): 0%*	• G/P (12): [redacted] • SOF/VEL (12): 100.0% (5/5)[e] • SOF + peg-IFN + RBV (12): 50% (1/2)[h] • Best supportive care (watchful waiting): 0%*	• G/P (8): [redacted][l] • SOF/VEL (12): 100.0% (11/11)[e] • Best supportive care (watchful waiting): 0%*	• G/P (12): [redacted][l] • SOF/VEL (12): 100.0% (11/11)[e] • SOF + peg-IFN + RBV (12): 50% (1/2)[n] • Best supportive care (watchful waiting): 0%*
6	• G/P (8): [redacted] • SOF/VEL (12): 100.0% (35/35)[e] • Best supportive care (watchful waiting): 0%*	• G/P (12): [redacted] • SOF/VEL (12): 100.0% (6/6)[e] • SOF + peg-IFN + RBV (12) 50% (1/2)[h] • Best supportive care (watchful waiting): 0%*	• G/P (8): [redacted][l] • SOF/VEL (12): 100.0% (35/35)[e] • Best supportive care (watchful waiting): 0%*	• G/P (12): [redacted][l] • SOF/VEL (12): 100.0% (6/6)[e] • SOF + peg-IFN + RBV (12): 50% (1/2)[n] • Best supportive care (watchful waiting): 0%*

Source: CS, Tables 59, 65 and 66, pages 148-163.
*) For best supportive care (no treatment), the SVR rate is assumed to be 0% (CS, Page 156)

Geno -type	Treatment (duration in weeks)			
	TN		TE	
	NC	CC	NC	CC

[a]For the sake of simplicity the model assumes all patients receive a 12 week treatment duration without RBV; [b]TA365 for OBV/PTV/RTV ± DSV was published before the results from TURQUOISE-III and AGATE-I became available and the NICE recommendation therefore stipulates the use of OBV/PTV/RTV ± DSV with RBV for GT1b patients with CC, and OBV/PTV/RTV + RBV for GT4 CC patients for 24 weeks. Subsequently, TURQUOISE-III demonstrated the efficacy of treatment with OBV/PTV/RTV + DSV for 12 weeks without RBV in GT1b patients with CC,[78] and AGATE-I demonstrated the efficacy of OBV/PTV/RTV + RBV for 12 weeks in GT4 patients with CC.[73] The licence for OBV/PTV/RTV ± DSV now reflects this. Therefore OBV/PTV/RTV + DSV without RBV for 12 weeks is used as the comparator in the economic analysis of this submission for GT1b patients with CC, and OBV/PTV/RTV + RBV for 24 weeks is used for GT4 CC patients; [c]SVR in GT1 patients is calculated using a weighted average of SVRs in GT1a and GT1b patients, and n/N is not reported; [d]For simplicity, the model assumes all patients receive EBR/GZR for 12 weeks; [e]Data available included the following: (i) SVR data stratified by cirrhosis status for TN and TE patients combined and (ii) overall SVR data stratified by TN and TE patients. The former were used and it was assumed that TN=TE; [f]'RBV-eligible' patients; [g]The number of GT4 NC and CC patients was calculated, assuming the percentage of CC patients was the same between GT4 and GT6 patients. The percentage of CC patients among GT4 and GT6 patients was calculated from the percentage of patients among the GT1, GT4 and GT6 patient population available in the trial publication[85, 88] and the percentage of patients among the GT1 population available in the US package insert.[138] The calculated n/N is reported to 2 decimal places; [h]Data for overall GT4, GT5 and GT6 population; [i]Data are weighted among null response, partial response and prior relapse patients; [k]Assumed to be the same as for TN; [l]There were low numbers of GT4, GT5 and GT6 TE patients recruited, so pooled results from GT4-, GT5- and GT6-infected patients were used; [m]In GT4 F4 where SVR≠100%, only the consolidated 'N' is reported; [n]Assumed to be the same as TN (data for overall GT4, GT5 and GT6 population), same assumption as TA430.[139]

CC = compensated cirrhosis; CSR = clinical study report; DAA = direct-acting antiviral; DCV = daclatasvir; DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/ pibrentasvir (300 mg/120 mg); GT = genotype; GZR = grazoprevir; IFN = interferon; ITT = intention-to-treat; ITT-PS = ITT mono-infected GT1 DAA-naïve; LDV = ledipasvir; NC = non-cirrhotic; OBV = ombitasvir; Peg-IFN = pegylated-IFN; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TN = treatment-naïve; VEL = velpatasvir.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company concludes that it is not feasible to form any network between G/P and any relevant comparator therapies; therefore, an indirect treatment comparison is not possible. The company then suggests the use of matching-adjusted indirect comparison (MAIC). However, this was not considered useful because most active interventions achieve SVR12 rates approaching 100%, requiring large sample sizes to detect any statistically significant differences in SVR12 rates; and because many baseline characteristics, necessary for adjusting response rates, are not available for comparators at subgroup levels.

Ultimately, the company uses naïve indirect comparisons to inform treatment effect estimates. The company acknowledges that this is associated with limitations, but does not describe any of these limitations. In fact, the section in the CS describing the uncertainties in the indirect and mixed treatment comparisons consists of two words: "Not applicable".

The company does not present any information about how response and adverse events for comparator studies were selected; whether all possible sources were used or how results were combined when multiple sources were available. In addition, no results for any of the comparator interventions are described in section B.2 (Clinical Effectiveness). Results of comparator interventions are only reported as inputs for the economic model (Section B3.3 Clinical parameters and variables); here, results for SVR (CS, Tables 65 and 66) and AEs (Tables 68 and 69) are reported without any references to differences between studies, apart from the main subgroup (genotype, TE vs TN, and NC vs CC). In most cases, the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C[139]); in fact the company presents two tables describing inputs that are different from TA430 (CS, Table 64 for SVR rates, and Table 67 for AE rates).

Therefore, the same critique[140] applies as for TA430:

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 of one particular SVR rate within a study is arbitrary and therefore subject to bias.

In addition, as described above, the company uses naïve indirect comparisons to inform treatment effect estimates in the economic model. Effect estimates are taken from single arms of included studies. This naïve indirect comparison is not adjusted for any differences between studies because the majority of publications do not provide the breakdown of baseline patient characteristics at the subgroup level (i.e. by genotype, treatment experience and cirrhosis status).

Although the ERG agrees that it is not feasible to form any network between G/P and any relevant comparator therapies and that the limited availability of baseline characteristics for comparator studies precludes an adjusted analysis, it should be taken into account that the results of these naïve indirect comparisons are unreliable.

The DSU describes the recommended methods for population-adjusted indirect comparisons in submissions to NICE in their report NICE DSU TSD 18.[141] On page 56 of TSD 18, the DSU states: '*The size of this systematic error can certainly be reduced, and probably substantially, by appropriate*

use of MAIC or STC. Much of the literature on unanchored MAIC and STC acknowledges the possibility of residual bias due to unobserved prognostic variables and effect modifiers; however, it is not made clear that the accuracy of the resulting estimates is entirely unknown, because there is no analysis of the potential magnitude of residual bias, and hence no idea of the degree of error in the unanchored estimates. It is, of course, most unlikely that systematic error has been eliminated. Hoaglin,[142, 143] in a series of letters critiquing an unanchored comparison by Di Lorenzo et al.[144] based upon a matching approach similar to MAIC, remarked that, without providing evidence that the adjustment compensates for the missing common comparator arms and the resulting systematic error, the ensuing results 'are not worthy of consideration'.'[141]

If the results of a poorly performed adjusted simulated treatment comparison based on single arm studies (unanchored) are 'not worthy of consideration', surely the results of a naïve comparison without any attempt at adjustment are even less worthy of consideration.

4.5 Additional work on clinical effectiveness undertaken by the ERG

An ideal approach would be to present results separately for head-to-head comparisons with other active comparators. However, only one of the studies used in the economic model included an active comparator: the ENDURANCE-3 trial. However, ENDURANCE-3 included three arms (G/P-12w, SOF+DCV-12w and G/P-8w) and patients were randomised to two of the three arms: G/P-12w versus SOF+DCV-12w. After enrolment in these two arms was complete, new patients were assigned to receive G/P for eight weeks. Therefore, G/P-8w is not part of the randomised comparison and G/P-12w is not in line with the anticipated licence for patients in this trial. This means there is no direct comparative evidence for G/P versus any of the comparators mentioned in the scope, apart from the two CERTAIN trials. Since these trials were in Japanese patients only, these were not considered by the company to be generalisable to the UK population.

As explained in Section 4.2, we will present a summary of the two CERTAIN studies in this section.

4.5.1 CERTAIN-1

The CERTAIN-1 trial (NCT02707952) was a Phase III, partially-randomised, open-label, multicentre study to evaluate the efficacy of G/P in Japanese adults with CHC, composed of two sub-studies.[64-66] The objectives of the study were to determine the safety and efficacy of G/P treatment in CHC.

Sub-study 1 was a randomised study in GT1-infected NC patients. Patients without Y93H polymorphisms were randomised at a 2:1 ratio to receive either eight weeks of treatment with G/P (300 mg/120 mg) or 12 weeks of treatment with OBV/PTV/RTV. All patients with Y93H polymorphisms were enrolled to receive eight weeks of treatment with G/P (300 mg/120 mg).

Sub-study 2 was a non-randomised study in GT1- or GT2-infected CC patients; GT3-, GT4-, GT5-, or GT6-infected NC and CC patients; GT1- or GT2-infected NC and CC patients who had failed prior DAA treatments; and GT1- or GT2-infected patients with severe renal impairment and CC. All patients were enrolled to receive G/P (300 mg/120 mg) for 12 weeks. Finally, GT1- or GT2-infected NC patients with severe renal impairment received G/P (300 mg/120 mg) for eight weeks.

Two hundred and ninety-five patients were enrolled. The primary efficacy endpoint tested the non-inferiority of the SVR12 rate in the eight-week G/P arm to the 12-week OBV/PTV/RTV arm in sub-study 1. The secondary efficacy endpoints were in line with the studies in the previous Section (SVR12 rate in each study arm, percentage of patients with on-treatment virologic failure and post-treatment relapse). Additional outcomes included safety, resistance, and patient reported outcomes (PROs).

In CERTAIN-1, the primary efficacy analysis was the percentage of GT1-infected NC patients in the ITT population of sub-study 1 without Y93H polymorphisms who achieved SVR12. This was 99.1% (two-sided 95% CI 97.2% to 100.0%) following eight weeks of treatment with G/P, and 100% [redacted] following 12 weeks of treatment with OBV/PTV/RTV. Further results for this study are not reported in the company submission. The CSR shows that a SVR12 rate of [redacted] was achieved in HCV GT3-infected patients with compensated cirrhosis or without cirrhosis and with or without prior pegylated IFN/ribavirin experience who were treated with 12 weeks of G/P.[64] This was [redacted].

The fixed-dose combination of G/P 300 mg/120 mg QD administered for eight and 12 weeks was well tolerated by Japanese patients including those without cirrhosis, with compensated cirrhosis, and with severe renal impairment, including those on dialysis. A similar safety profile was observed between HCV GT1-infected, DAA treatment-naïve, Japanese patients treated with either G/P 300 mg/120 mg QD administered for eight weeks or OBV/PTV/RTV QD for 12 weeks. Overall, among patients treated with G/P, the most common (≥ 5.0% of patients) TEAEs were nasopharyngitis, pruritus, and headache.[64]

4.5.2 CERTAIN-2

The CERTAIN-2 trial (NCT02723084) was a Phase III, randomised, open-label, multicentre study to evaluate the efficacy of G/P in Japanese NC adults with chronic GT2 HCV infection.[64, 67-69] The objectives of the study were to determine the safety and efficacy of G/P treatment.

GT2-infected NC DAA-TN patients were randomised at a 2:1 ratio to receive G/P (300 mg/120 mg) for eight weeks or SOF + RBV for 12 weeks. 136 patients were enrolled. The primary efficacy endpoint tested the non-inferiority of the SVR12 rate in the eight-week G/P arm to the 12-week SOF + RBV arm. The secondary efficacy endpoints were in line with CERTAIN-1.

In CERTAIN-2, the SVR rate among GT2-infected DAA-TN patients without cirrhosis 12 weeks after treatment with G/P for eight weeks was 97.8% (two-sided 95% CI 94.7% to 100.0%), and 93.5% [redacted] with SOF + RBV for 12 weeks. Further results for this study are not reported in the company submission.

The fixed dose combination of G/P 300 mg/120 mg QD administered for eight weeks was well tolerated by Japanese patients with HCV GT2 infection without cirrhosis. Patients treated with G/P treatment had fewer overall TEAEs and TEAEs related to treatment compared to SOF + RBV treatment. Patients treated with SOF + RBV had higher rates of anemia, hyperbilirubinemia, and hyperuricemia. Overall among patients treated with G/P, the most common (≥ 5% of patients) TEAEs were nasopharyngitis, headache, and malaise. No TEAE related to treatment was reported in > 5% of patients treated with G/P. The most common (≥ 5% of patients) TEAEs reported among patients receiving SOF + RBV were anemia, blood bilirubin increased, malaise, nasopharyngitis, nausea, stomatitis, and hyperuricemia. TEAEs related to SOF + RBV reported in > 5% of patients included anemia and blood bilirubin increased. The higher rates of these events related to SOF + RBV are likely due to the effect of RBV.[69]

4.6 Conclusions of the clinical effectiveness section

The conclusion from the G/P studies is that G/P has high SVR rates in all genotypes. In addition, G/P has a relative favourable safety and tolerability profile. However, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each subgroup. Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators relies on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. In most cases, the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C[139]). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS: measurement and evaluation of health effects; and cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.

Searches for cost effectiveness analysis review

A systematic literature review was conducted to identify evidence to support the cost and cost effectiveness of novel DAAs for HCV. The systematic literature review was undertaken in April 2017 and was an update to the systematic literature review performed for TA430.[139] No date limits were indicated in the search strategies, but it was stated in Appendix G that databases were searched from 2016 to present.[16] There were no language limits. Searches were carried out in PubMed, Embase, Tufts Cost Effectiveness Analysis (CEA) Registry, HTA database, NHS EED and EconLit. In addition, supplementary searches were undertaken from 2016 to present in AASLD, EASL, ISPOR, The Viral Hepatitis Congress and the Asian Pacific Association for the Study of the Liver.

ERG comment: In response to a clarification question about the correct PRISMA figures for the cost effectiveness Embase search, the company confirmed that an incorrect search strategy had been submitted in error and the correct strategy was consequently presented.

The ERG noted that a UK country search filter had been added to the updated Embase and PubMed strategies, and were concerned that a number of relevant records may have been missed as the filter was not sufficiently comprehensive to have picked up all UK records. The ERG also noted that the updated Embase search strategy continued to make ineffective use of parentheses and lacked relevant EMTREE terms. It is therefore possible that relevant evidence has still been missed.

The ERG commented that PubMed searches may have used wildcard symbols which were not supported by PubMed and therefore results may have been compromised. In response the company re-ran searches but no new records were identified.

The ERG felt the use of a cost filter was unnecessarily restrictive to be applied in the Cochrane Library which is a study design specific resource. Consequently, the company re-ran searches in the HTA database and NHS EED without a cost filter. This resulted in two new records, neither of which were relevant.

Measurement and valuation of health effects

A separate systematic literature search was conducted for health-related quality-of-life benefits of DAAs for HCV and was reported in detail in Appendix H.[16] Searches were undertaken in PubMed, Embase, EconLit, CDSR, DARE, CENTRAL, HTA database and NHS EED from 2016 to April 2017. As before, this systematic literature review was an update of TA430.[139] In addition, supplementary searches for conference proceedings from 2016 to present were conducted in AASLD, EASL, ISPOR, The Viral Hepatitis Congress and the Asian Pacific Association for the Study of the Liver.

ERG comment: The ERG raised an issue in the clarification letter that findings in Embase searches in Appendix H for health-related quality of life studies were unexpectedly low (n=321) and that this was most likely the result of a Boolean NOT operator being applied inappropriately.[13] The company explained that this number was a test set and that screening was done on a full set.[17] However, the PRISMA flowchart indicates that 321 Embase results were screened for health-related quality of life studies and the response to clarification did not provide further evidence or additional numbers for the full set of Embase results. The ERG remains unconvinced that this search was run adequately and it therefore remains possible that evidence has been missed.

Cost and healthcare resource identification, measurement and valuation

A systematic literature review was conducted on resource use of novel DAAs for HCV from 2016 to April 2017 on PubMed, Embase, EconLit, CDSR, DARE, CENTRAL, HTA database and NHS EED. As with previous sections, supplementary searches for conference proceedings were undertaken from 2016 to present in AASLD, EASL, ISPOR, The Viral Hepatitis Congress and the Asian Pacific Association for the Study of the Liver. The searches were an update of TA430 as the research question was the same for both appraisals.[16, 139]

ERG comment: In response to queries about the use of wildcard characters which are not supported in PubMed, the company re-ran PubMed searches in Medline (Ovid). A more comprehensive UK country filter was applied in this search and the ERG was satisfied that most UK records were likely to have been found. An English language limit was also applied and, although this is not recommended practice, the company was looking specifically for UK records, so it is likely that no relevant records were missed with this limit.

5.1.2 Inclusion/exclusion criteria used in the study selection

The eligibility criteria for the economic systematic literature review were summarised in Table 213 from the Appendix G of the company submission.[16] The eligibility criteria for inclusion/exclusion can be classified into six main classes as below:

- Language: only studies in English language are included.
- Study design: cost-consequence, cost-minimisation, cost effectiveness, cost-utility and cost-benefit studies are included. Review studies, letters to the editors or other comments are excluded.
- Population: studies with chronically infected HCV adult patients (older than 18 years old) with genotypes 1 to 6 are included.
- Interventions: Following IFN free regimens: G/P, SOF/VEL, EBR/GZR (with or without RBV), LDV/SOF (with or without RBV), OBV/PTV/RTV (with or without RBV), OBV/PTV/RTV+DSV (with or without RBV), DCV/SOF (with or without RBV), SOF/RBV and following IFN-containing regimens are included: DCV/PR, SMV/PR, SOF/PR and PR. Other DAA combinations, with or without PR are excluded.
- Outcomes: no exclusion based on outcomes
- Comparators: no exclusion based on comparators

ERG Comments: 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

Seven studies were identified from the electronic database and conference proceeding abstract search described in Section 5.1.1. The number of excluded studies and their reasons of exclusion were summarised in the PRISMA diagram given in Figure 32 (Appendix G of the CS). Two recent NICE TAs, TA430 and TA413 were also included, which resulted in nine cost effectiveness studies published after 2016.[139, 145-152]

The summary and quality assessment of these nine studies, together with the studies identified by the SLR performed for TA430, were provided in Table 214 and in Table 215 from the Appendix G of the CS. None of these identified studies evaluated the cost effectiveness of G/P. Due to the lack of studies on the cost effectiveness of G/P, the company suggested that a de novo analysis was required.

Also, even though they were not identified in the SLR, the company provided a brief summary for the following three UK based cost effectiveness studies: Wright et al. (2006), Shepherd et al. (2007) and Hartwell et al. (2011).[153-155] These studies guided the company in the development of model structure and selection of inputs.

ERG comment: The cost effectiveness literature review in this submission was conducted as an update of the systematic literature review (SLR) conducted in TA430. This approach is based on a full reliance on the SLR results in TA430, not only in terms of search strategy but also the review process and reviewers. The ERG considers that this approach might be prone to missing/excluding potentially relevant articles that were missed/excluded in TA430.

Furthermore, it was not clear to the ERG how the three UK based cost effectiveness studies (Wright et al. 2006, Shepherd et al. 2007 and Hartwell et al. 2011) were identified.[153-155] The ERG has doubts if these were the only UK based cost effectiveness analyses that could have informed the CS model structure/choice of inputs and considers that the selection of these studies could have been based on a systematic, reproducible procedure.

5.1.4 Conclusions of the cost effectiveness review

No specific conclusions from the economic review were provided in the CS. The ERG considers that the identified studies might contain valuable information regarding costs, utilities and model structure, but that they do not negate the necessity of developing a de novo model for the current comparison.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.1 presents a summary of the *de novo* economic model developed by the company.

Table 5.1: Summary of the company submission economic evaluation

	Approach	Source/Justification	Signpost (location in CS)
Model	A cost effectiveness model that consist of a Markov cohort model describing the long-term disease progression of chronic HCV. The model takes into account the main efficacy outcome SVR12, as evaluated in the clinical trials. The same model structure is used for all subpopulations. Patients initiated treatment at the start of the first year.	The economic model aimed to reflect the clinical pathway of care for patients with chronic HCV. The modelling approach is in line with the modelling approaches in previous NICE technology assessments. [145, 156]	Section B.3.2.2
Sub populations	Twenty-six subpopulation groups were considered based on categories below: • genotypes: GT1, GT2, GT3, GT4, GT5 and GT6 • treatment-naïve (TN) and treatment-experienced (TE). • cirrhotic (C) and non-cirrhotic (NC) • IFN eligibility (only for GT2 and TN patients) This categorisation resulted in the following subpopulations: 1. GT1, TN, C 2. GT1, TN, NC 3. GT1, TE, C 4. GT1, TE, NC 5. GT2, TN, C, IFN eligible 6. GT2, TN, C, IFN ineligible 7. GT2, TN, NC, IFN eligible 8. GT2, TN, NC, IFN ineligible 9. GT2, TE, C 10. GT2, TE, NC 11. GT3, TN, C 12. GT3, TN, NC 13. GT3, TE, C 14. GT3, TE, NC 15. GT4, TN, C 16. GT4, TN, NC 17. GT4, TE, C	These subgroups were considered because of the differences in effectiveness and treatment duration of G/P between these subgroups, as well as the list of comparators and their effectiveness for each subgroup.	Section B.3.2.1

	Approach	Source/Justification	Signpost (location in CS)
	18. GT4, TE, NC 19. GT5, TN, C 20. GT5, TN, NC 21. GT5, TE, C 22. GT5, TE, NC 23. GT6, TN, C 24. GT6, TN, NC 25. GT6, TE, C 26. GT6, TE, NC		
States and events	The model consists of 13 health states. F0-F3 are noncirrhotic states and F4 was considered as cirrhotic state. • No HCV • F0: no fibrosis • F1: portal fibrosis without septa • F2: portal fibrosis with septa • F3: portal fibrosis with numerous septa • F4: compensated cirrhosis • SVR, history of mild fibrosis (F0-F1) • SVR, history of moderate fibrosis (F2-F3) • SVR history of compensated cirrhosis (F4) • DC: decompensated cirrhosis • HCC: Hepatocellular carcinoma • LT: Liver transplant (differentiated to first and subsequent years) • LV-Death: Liver related death associated with DC, HCC or liver transplantation • LV unrelated death Non-cirrhotic patients start from states F0-F3, and cirrhotic patients start from F4. All treatment related outcomes (achieving SVR, treatment related adverse events and discontinuation) occur within the first year of the model. Patients who do not achieve SVR are at risk of progressing to more severe states. Patients who reached F4 can progress to DC and HCC states, which may lead to liver transplantation and liver related death.	Health states were based upon disease severity and treatment effect. The treatment determines the SVR, adverse event and discontinuation probabilities.	Section B.3.2.2

	Approach	Source/Justification	Signpost (location in CS)
	Liver transplantation state was divided into two categories (first year and later years).		
Comparators	Comparators differ for each of the subpopulation. EBR/GZR (EBR and GZR 12w; subpopulations 1-4, 15-18) BSC-watchful waiting (subpopulations: 1-26) SOF/VEL (12 w, subpopulations: 1-6,8-26) LDV/SOF (8w, subpopulation 2; 12w, subpopulations 1, 3, 4, 15, 17 and 18) OBV/PTV/DSV+DSV ± RBV (12 w or 24w, subpopulations 1-4 and 15-18) PR (24 w, subpopulation 7) SOF/RBV: (12w, subpopulations: 6 and 8-10; 24w, subpopulations 11 and 13) DCV/SOF: (12w, subpopulations 12 and 14) DCV/SOF/RBV (24 w, subpopulations 11 and 13) SOF/PR (12w, subpopulations 11, 13 and 14)	They are mainly based on licensed indications and NICE recommendations, however in the submission not all comparators mentioned in the final scope were included. Some of the comparators in the NICE final scope (e.g. PR) were excluded based on expert advice from English clinicians as well as the June 2017 Eastern Liver Network Hepatitis C Guidelines (v8.1).[157]	Section B.3.2.3
Natural history	Natural history is based on how disease progresses when a patient does not reach SVR.	The progression rates between F0 and F4 were based on Thein et al. 2008, which is a systematic review and meta-analysis providing state specific progression rates.[158] GT specific hazard ratios from Kanwal et al. 2014 were applied.[159] Transition probabilities after DC are based on Cardoso et al. 2010 (transition to HCC from the recovered state) and Fattovich et al. 1997 (for all other transitions).[160]	Section B.3.3.3
Treatment effectiveness	Treatment influences the probability of reaching SVR, adverse events and discontinuation.	SVR, adverse event and discontinuation probabilities were based on naïve indirect comparison of clinical trials assessing the	Section B.3.3.2

	Approach	Source/Justification	Signpost (location in CS)
		efficacy of G/P and its comparators in the relevant subgroups.	
Adverse events	The adverse events considered in the economic model were anaemia, neutropaenia, rash, depression and thrombocytopenia. Only the cost consequences of these events were modelled.	These adverse events were selected by the company according to their frequency and impact on costs.	Section B.3.5.3
Health-related QoL	The model uses state based utilities from the literature (utilities that were used in Wright et al. and Ratcliffe et al. 2002).[161] A utility increment due to SVR is applied based on Shepherd et al. 2007 and Hartwell et al. 2011.[154] Treatment-related health utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events.	Those state-based health utility values were used in previous submissions.	Section B.3.4
Resource utilisation and costs	Treatment cost (e.g. technology acquisition and administration costs of G/P and other comparators, monitoring costs and tests) and health state costs (disease management costs based on disease stage) and other costs for adverse events.	Based on literature, expert opinion and UK reference costs and previous appraisals (especially TA430).	Section B.3.5
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case.	Section B.3.2.2
Sensitivity analysis	One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analysis	Ranges based on observed confidence intervals and assumptions.	Section B.3.8

AE: Adverse event; BSC: best supportive care; C: cirrhosis; DC: Decompensated cirrhosis; DCV: daclatasvir; EBR: Elbasvir; F: Fibrosis; GT: genotype; GZR: grazoprevir; HCC: Hepatocellular carcinoma; HCV: hepatitis C virus; LDV: ledipasvir; LT: liver transplantation; NC: non-cirrhosis; NHS: National Health Services; PLT: post-liver transplantation; PR: pegylated interferon and ribavirin; SOF: sofosbuvir; SVR: sustained virological response; TE, treatment-experienced; TN, treatment-naïve; w: week; WTP, willingness to pay; CS = Company submission; NICE = National Institute for Health and Care Excellence; QALY = National Institute for Health and Care Excellence; TA = Technology Appraisal; UK = United Kingdom.

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.2: Comparison of company submission model to the NICE reference case

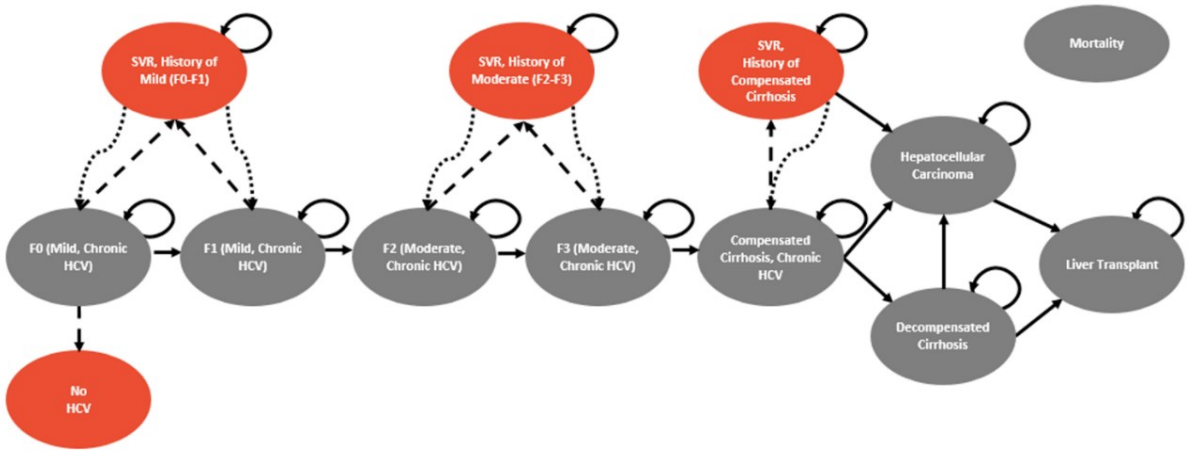
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	No	Some of the treatments specified in the final scope were excluded based on clinic experts and Eastern Liver Network Hepatitis C Guidelines (v8.1).[157]
Type of economic evaluation	Cost effectiveness analysis	Yes	Half-cycle correction not considered in the analysis.
Perspective on costs	NHS and PSS	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	
Synthesis of evidence in outcomes	Systematic review	Yes/partially	Most parameters were based on systematic review; however, comparative effectiveness is based on naïve indirect comparison. Some parameters were identified by a non-systematic search (referring to previous appraisals).
Measure of health effects	QALYs	Yes	
Source of data for measurement HRQoL	Reported directly by patients and/or carers.	Yes	
Source of preference data for valuation of changes in HRQoL	Sample of public	Yes	
Discount rate	Annual rate of 3.5% on costs and health effects	Yes	
Equity weighting	No special weighting	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	

HRQoL = Health-related Quality of Life; NHS = National Health Services; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = Quality-adjusted Life Year

5.2.2 Model structure

A cohort Markov state-transition model was developed for this submission. The structure of the model relied on published models of the natural history of HCV infection, including a model previously developed by the company for 2D or 3D for the NICE technology appraisal TA365.[145, 155, 156, 162] The model structure is depicted in Figure 5.1, where "recovered" health states are represented by red ellipses, "non-recovered" health states by grey ellipses, solid arrows represent transitions between health states, hashed arrows depict the possibility of achieving SVR, and dotted arrows depict a potential re-infection. However, as explained below, not all potential transitions depicted in Figure 5.1 are possible in practice.

Figure 5.1: Post-treatment, natural disease progression phase schematic



DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HCV = hepatitis C Virus; LT = liver transplant; SVR = sustained virologic response. Source: Figure 15 in the CS.[2]

Further assumptions made by the company regarding the economic model's structure are summarised below.

Treatment phase

In the initial treatment phase of the model, the efficacy of the initial antiviral treatments is captured by estimating the proportion of patients who achieve SVR. The model distinguishes between non-cirrhotic (NC) and cirrhotic patients. NC patients are further stratified by fibrosis severity (F0– F3). The model assumes that all cirrhotic patients in the treatment phase have compensated cirrhosis (CC). This is because G/P is not licensed for use in patients with decompensated cirrhosis (DCC). Initially, all patients are on treatment for the first cycle (one year) of the model. Since the duration of all HCV treatments is short (e.g. 8–16 weeks for G/P), it is assumed that all direct treatment-related costs and effects are captured within the first cycle. The company's model also assumes that patients cannot progress or die in the weeks while on treatment. This is in line with previous HCV models.[147, 156] Patients for whom treatment is deemed successful are assumed to achieve SVR. Otherwise, they are assumed to be at risk of progressive liver disease as if they were untreated.[153]

Natural history phase

The natural history phase of the model considers the lifetime disease progression of patients with HCV. The company assumed that spontaneous remission of HCV was not possible. Thus, the transition probability from F0 to "no HCV" is zero in the model. This assumption was justified on page 144 in the CS due to the "*low probability of spontaneous clearance of HCV infection*".[2] The model also assumes that patients achieving SVR enter one of three possible "recovered" health states, depending

on their fibrosis history (SVR with history of mild [F0–F1] fibrosis, SVR with history of moderate [F2–F3] fibrosis, or SVR with history of CC [F4]). Patients who enter the mild or moderate "recovered" health states are assumed to remain there until they die (i.e. the re-infection probability is assumed zero). Thus, patients who achieve SVR with a history of mild or moderate CHC cannot progress to more severe liver disease health states. This assumption is supported by clinical data.[163-168] However, patients with a history of CC, even after achieving SVR, can still transition to the HCC health state. This assumption is also based on clinical evidence.[167-172] Patients who do not achieve SVR are considered as if they were untreated and can remain in the ("non-recovered") health states (defined by their fibrosis history) or progress to more severe disease health states (DCC, HCC, and liver transplant [LT]). Finally, death is also included as a health state in the model and it can be reached from any other health state. It is defined by general mortality rates based on national life tables.[173] In addition, liver-related death is possible from the DCC, HCC and LT health states only, as these states are considered to have increased mortality risks.[154, 155, 174, 175]

Re-infection and onward transmission

The company's model does not include the probability of re-infection (dotted arrows in Figure 5.1) and the risk of onward transmission. This approach was previously accepted by NICE.[176]

ERG comment: The model structure in the CS is in line with the clinical pathway of care for CHC. Deviations from this, such as not modelling subsequent lines of treatment, have been explained by the company. It is also in line with previous economic models submitted to NICE (TA364 and TA413),[147, 177] where four mild/moderate fibrosis health states of increasing METAVIR scores, CC, DCC, HCC, LT and death are included in the model structure.

Patients who do not achieve SVR are considered as if they were untreated,[153] although in clinical practice these patients may receive further lines of treatment. The company claimed on page 144 of the CS that the "*re-treatment pathway is not well-defined*" and the assumptions required to model re-treatment would result in additional uncertainty to the model results.[2] The ERG considers the first part of the sentence unclear and, while agreeing with the second part, additional uncertainty should be captured in the probabilistic analyses. The company also mentions that, since the success rates of treatment are high, the proportion of patients who experience treatment failure is low. Therefore, the company does not expect this to have a major impact on the model results. While the ERG agrees with this, it should be emphasised that this applies to the deterministic results. Not including further lines of treatments is likely to underestimate the overall uncertainty in the company's model. In the context of cost effectiveness analyses with multiple comparators this might have significant consequences on the probabilistic results. Nevertheless, the assumption of not modelling further lines of treatment is consistent with economic models that have been previously appraised by NICE.[139, 147, 156]

Patients who do not achieve SVR can progress to more severe disease health states (DCC, HCC, and liver transplant [LT]). In line with previous models, DCC is modelled as a single health state,[145, 155, 162, 178] although the company acknowledged in their submission (page 144) that "*DCC can present simultaneously in multiple forms in any individual patient*".[2] This is a limitation of the current modelling approach, which does not account for patient heterogeneity. Two separate health states are considered for HCC: one for the first year and one for subsequent years. However, the input parameters associated to these health states are the same in all economic analyses. Therefore, in practice there is no distinction between the two health states. Patients with DCC or HCC may transition to LT. The LT probability of death is different for the first year and for subsequent years and it is modelled as two different health states.

In line with previous approaches accepted by NICE,[176] the company did not include onward transmission and the probability of re-infection in their cost effectiveness model. The ERG agrees with the company that modelling onward transmission would not fit into a common Markov model. However, re-infection probabilities have been excluded from the model without any proper justification. The company claims (on page 145 in the CS) that including onward transmission in the model is likely to result in lower ICERs for active treatments,[2] in particular, for those that are most effective and for which onward transmission would be most reduced. In contrast, re-infection is likely to result in higher ICERs for active treatments since patients who achieved SVR would be in risk of advancing to more severe health states without the possibility of re-achieving SVR (given that subsequent therapies are not included in the model). The company also refers to Madin-Warburton et al. 2016 where it is shown that "*there is a net positive impact on cost effectiveness in a dynamic transmission model for treatment of HCV infection of incorporating both re-infection and onward transmission"*.[179] Based on these, the company concluded (on page 145 in the CS) that their model "*may represent a conservative approach that under-estimates the cost effectiveness of active treatments including G/P*".[2] While this conclusion might be correct, the ERG considers that it is not possible to determine the extent to what this approach is indeed conservative or not.

5.2.3 Population

The patient population considered in the company's economic analyses was adults with CHC. Results are presented for 26 different subgroups, which are characterised by HCV genotype, treatment history and fibrosis status. There are six different HCV genotypes (GT1-GT6), each with different characteristics (see also Section 2 of this report). Treatment history distinguishes between treatment-naïve and treatment-experienced patients where the latter are defined as patients who have not adequately responded to prior IFN/RBV-based treatment with or without SOF. This is in line with the clinical trial programme of G/P (see Section B.2 in the CS).[2] Fibrosis status considers non-cirrhotic patients (i.e. patients with METAVIR score F0-F3) and patients with compensated cirrhosis (i.e. patients with METAVIR score F4). Analyses for IFN-ineligible versus IFN-eligible patients are conducted for GT2 treatment-naïve patients only. However, it should be noted that the only differences between the IFN-eligible and IFN-ineligible patients are the comparators considered for the economic analyses, i.e. the SVR or AE rates are not adjusted according to IFN-eligibility. Furthermore, GT1a and GT1b subgroups are not differentiated in the company's model. A summary of the subgroups included in the CS is presented in Table 5.3.

Table 5.3: Population subgroups considered in the company's economic analyses

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	✓	✓	✓	✓
GT2	IFN-eligible: ✓ IFN-ineligible: ✓	IFN-eligible: ✓ IFN-ineligible: ✓	✓	✓
GT3	✓	✓	✓	✓
GT4	✓	✓	✓	✓
GT5	✓	✓	✓	✓
GT6	✓	✓	✓	✓

Source: Table 56 in the CS.[2]
GT = genotype; IFN = interferon

The baseline characteristics used in the base-case health economic analyses were obtained from the Adelphi Chart Tracking Study, a market research performed amongst 75 specialist healthcare professionals in the UK.[180] The results of the study are summarised in Table 5.4.

Table 5.4: Baseline characteristics

Variable	Treatment-naïve		Treatment-experienced		Source
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis	
Age (years)	43		45		Adelphi Research UK (2017)[180]
Male (%)	66		71		
F0 (%)	35.9	0	32.1	0	
F1 (%)	45.7	0	33.6	0	
F2 (%)	14.7	0	23.2	0	
F3 (%)	3.8	0	11.1	0	
F4 (%)	0	100	0	100	
Source: Table 61 and 62 in the CS.[2] F = fibrosis severity (METAVIR score)					

ERG comment: The population considered in the company's economic analyses is in line with the NICE scope. The rationale for including (or excluding) subgroups in the analyses is described in Section 3.5 of this report.

Distinction based on IFN-eligibility was only considered for GT2 TN patients. This was because GT2 is the genotype in which the SOF/VEL recommendation is restricted on the basis of IFN-eligibility. Therefore, the company considered that GT2 is the genotype for which the question of IFN-eligibility remains a key consideration. However, treatment and patient characteristics and costs are assumed to be the same regardless of IFN-eligibility. The only difference in the economic analyses was the comparators included in the analysis. Furthermore, the clinical trials for G/P did not stratify patients by IFN-eligibility.

The company did not distinguish GT1 patients by subtype (1a and 1b). The company considered that since GT1a and GT1b patients are treated similarly with G/P, and the difference in response between GT1a and GT1b is small, it is unlikely that this becomes a major issue from both a clinical and cost effectiveness perspective. This assumption represents a pragmatic approach, and it has been previously considered acceptable by Evidence Review Groups (ERGs) as part of NICE appraisals in this indication.[176] Moreover, this assumption is also in line with G/P licence.

5.2.4 Interventions and comparators

The intervention considered in the company's economic model is G/P, which recently received marketing authorisation from the EMA. The licensed dose is 300 mg/120 mg OD, with the recommended treatment durations shown in Table 5.5. Thus, the intervention is in line with the scope.

Table 5.5: Treatment duration for licence

Patient population	8 weeks for all genotypes	CC
TN	GT1,2, 4–6: 8 weeks GT3: 16 weeks	12 weeks for all genotypes
TE, previously treated with: Peg-IFN + RBV SOF + peg-IFN + RBV SOF + RBV	8 weeks for all genotypes	GT1, 2, 4–6: 12 weeks GT3: 16 weeks
Source: Table 58 in CS.[2] CC, compensated cirrhosis; GT, genotype; NC, non-cirrhotic; peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve		

The company determined the comparators included in the economic analyses based on "*consideration of NICE-approved treatments for CHC, expert advice from English clinicians, and the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1)*".[157] These comparators were included in the model as per their marketing authorisations and licensed doses (as recommended by NICE). The comparators considered in the CS are summarised by subgroup genotype in Table 5.6. The included comparators are in line with the scope; however, some of the comparators mentioned in the scope are excluded from the economic analyses.

Table 5.6: Comparator treatments per subgroup

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	CC	NC	CC
1	SOF/VEL (12) EBR/GZR[a] (12) SOF/LDV (8) OBV/PTV/RTV + DSV (12), 1a: + RBV Best supportive care (watchful waiting)	SOF/VEL (12) EBR/GZR[a] (12) SOF/LDV (12) OBV/PTV/RTV + DSV (12), 1a: (24) + RBV[b] Best supportive care (watchful waiting)	SOF/VEL (12) EBR/GZR[a] (12) SOF/LDV (12) OBV/PTV/RTV + DSV (12), 1a: + RBV Best supportive care (watchful waiting)	SOF/VEL (12) EBR/GZR[a] (12) SOF/LDV (12) OBV/PTV/RTV + DSV (12), 1a: (24) + RBV[b] Best supportive care (watchful waiting)
2	Comparators for IFN-eligible patients: Peg-IFN + RBV (24) Best supportive care (watchful waiting) Comparators for IFN-ineligible patients:	Comparators for IFN-eligible patients: SOF/VEL (12) Best supportive care (watchful waiting) Comparators for IFN-ineligible patients: SOF/VEL (12) SOF + RBV (12)	SOF/VEL (12) SOF + RBV (12) Best supportive care (watchful waiting)	SOF/VEL (12) SOF + RBV (12) Best supportive care (watchful waiting)

Genotype	Treatment (duration in weeks)			
	TN		TE	
	NC	CC	NC	CC
	SOF/VEL (12) SOF + RBV (12) Best supportive care (watchful waiting)	Best supportive care (watchful waiting)		
3	SOF/VEL (12) SOF + DCV (12) Best supportive care (watchful waiting)	SOF/VEL (12) SOF + DCV + RBV (24) SOF + peg-IFN + RBV (12) SOF + RBV (24) Best supportive care (watchful waiting)	SOF/VEL (12) SOF + DCV (12) SOF + peg-IFN + RBV (12) Best supportive care (watchful waiting)	SOF/VEL (12) SOF + DCV + RBV (24) SOF + peg-IFN + RBV (12) SOF + RBV (24) Best supportive care (watchful waiting)
4	SOF/VEL (12) EBR/GZR[a] (12) OBV/PTV/RTV + RBV (12) Best supportive care (watchful waiting)	SOF/VEL (12) EBR/GZR[a] (12) SOF/LDV (12) OBV/PTV/RTV + RBV (12)[b] Best supportive care (watchful waiting)	SOF/VEL (12) EBR/GZR[a] (12) SOF/LDV (12) OBV/PTV/RTV + RBV (12) Best supportive care (watchful waiting)	SOF/VEL (12) EBR/GZR[a] (12) SOF/LDV (12) OBV/PTV/RTV + RBV (12)[b] Best supportive care (watchful waiting)
5 or 6	SOF/VEL (12) Best supportive care (watchful waiting)	SOF/VEL (12) SOF + peg-IFN + RBV (12) Best supportive care (watchful waiting)	SOF/VEL (12) Best supportive care (watchful waiting)	SOF/VEL (12) SOF + peg-IFN + RBV (12) Best supportive care (watchful waiting)

Source: Table 59 in CS.[2]

[a] For the sake of simplicity the model assumes all patients receive a 12 week treatment duration without RBV.

[b] TA365 for OBV/PTV/RTV ± DSV was published before the results from TURQUOISE-III and AGATE-I became available and the NICE recommendation therefore stipulates the use of OBV/PTV/RTV ± DSV with RBV for GT1b patients with CC, and OBV/PTV/RTV + RBV for GT4 CC patients for 24 weeks. Subsequently, TURQUOISE-III demonstrated the efficacy of treatment with OBV/PTV/RTV + DSV for 12 weeks without RBV in GT1b patients with CC,[78] and AGATE-I demonstrated the efficacy of OBV/PTV/RTV + RBV for 12 weeks in GT4 patients with CC.[73] The licence for OBV/PTV/RTV ± DSV now reflects this. Therefore OBV/PTV/RTV + DSV without RBV for 12 weeks is used as the comparator in the economic analysis of this submission for GT1b patients with CC, and OBV/PTV/RTV + RBV for 24 weeks is used for GT4 CC patients.

CC, compensated cirrhosis; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; Peg-IFN, pegylated-IFN; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

ERG comment: The comparators included in the cost effectiveness analyses were mostly in line with the final scope. Discrepancies and excluded comparators were described in Section 3.3 of this report.

The company did not consider any treatment continuation rules for G/P or any relevant comparators. Although NICE guidance recommends SOF + DCV for GT3 NC patients with significant fibrosis only, the company took a pragmatic approach and included this treatment as a comparator for all GT3 NC patients.

5.2.5 Perspective, time horizon and discounting

The cost effectiveness analyses performed by the company adopted the perspective of the NHS/PSS. A discount rate of 3.5% was applied for both costs and utilities. A 70-year time horizon with an annual cycle length was assumed in the cost effectiveness model.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness parameters for the model were derived from the trial data described throughout Section 4 of this report. As explained in Section 5.2.2, two main types of transition probabilities can be distinguished in the model: SVR rates and natural disease progression transition probabilities. These are discussed in more detail below.

Sustained virologic response rates

SVR rates were obtained from clinical trial data. These were used to estimate the transition probabilities from baseline health states (mild fibrosis, moderate fibrosis or CC) to the corresponding "recovered" health state after successful treatment. In particular, the SVR rates (defined as HCV RNA <LLOQ) observed at 12 weeks after the end of treatment on the ITT population (denoted by SVR12) from the company and comparator clinical trials were used directly in the model. These are presented in Table 4.16 of this report. SVR rates are further stratified by fibrosis severity (NC [F0–F3] and CC [F4]) and HCV genotype (GT1 to GT6). Since in most of cases available data did not report different SVR rates for mild (F0-F1) and moderate (F2-F3) fibrosis, the available NC SVR rate was applied for both the mild and moderate fibrosis health states. Only for SOF/LDV in GT1 TN patients, SVR rates were obtained separately for patients with mild and moderate fibrosis.

ERG comment: The model uses the SVR12 rates obtained in RCTs with the various treatment options as model input for treatment effectiveness. As also discussed in Section 4 of this report the main concern is that data for SVR12 were taken from single arms. Therefore, the comparisons for SVR12 rates between G/P and comparators rely on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. The limitations of this input data necessarily lead to non-robust cost effectiveness outcomes.

In addition, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each subgroup. Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

Natural disease progression transition probabilities

Natural disease progression transition probabilities were derived from the literature. These were categorised in four different groups: fibrosis progression, non-fibrosis progression, liver transplantation and liver-related mortality. A brief description of each category and a summary of the annual transition probabilities used in the economic model are given below.

Fibrosis progression

The company considered a two-step approach where fibrosis progression transition probabilities for GT1 were calculated first using equations from Thein et al. 2008.[158] Subsequently, different literature-based hazard ratios were applied to obtain the transition probabilities for the genotypes GT2 to GT6.

The regression equations presented by Thein et al. 2008 were used to calculate stage-specific fibrosis progression rates as a function of the following covariates: duration of HCV infection (in years), age at infection (in years), gender (% male), genotype (% GT1), source of infection (intravenous drug use [IDU] or blood transfusion), excessive alcohol consumption (at least more than 20 g/day in the 12 months prior to study entry) and study design (cross-sectional/retrospective = 1; retrospective-prospective = 0).[158] These equations can be seen in Table 5.7 below.

Table 5.7: Equations to estimate fibrosis progression rates for GT1

Progression rate	Equation	Source
F0 to F1	$\exp(-\beta 1 + \beta 2 \times duration + \beta 3 \times design + \beta 4 \times male + \beta 5 \times genotype)$	Thein et al. (2008)[158]
F1 to F2	$\exp(-\beta 1 - \beta 2 \times duration + \beta 3 \times excess\ alcohol)$	
F2 to F3	$\exp(-\beta 1 + \beta 2 \times age - \beta 3 \times duration + \beta 4 \times excess\ alcohol)$	
F3 to F4	$\exp(-\beta 1 + \beta 2 \times age - \beta 3 \times duration + \beta 4 \times injecting\ drug\ users + \beta 5 \times blood\ transfusion + \beta 6 \times genotype)$	
Source: Page 177 in the CS.[2] exp = Exponential		

In order to estimate fibrosis progression rates for GT1, the equations above were populated with the patient baseline characteristics and the regression coefficients used in the base-case for TA364 (as reported in Table 72 and Table 73 in the CS, respectively).[2] The estimated fibrosis progression rates were converted to transition probabilities for GT1 by applying the following formula: transition probability = 1 – exp (rate). The hazard ratios used to obtain the transition probabilities for the genotypes GT2 to GT6 were based on Kanwal et al. 2014.[159] Despite being a non-UK study, the company used these hazard ratios since the applicability of this study to a UK setting was accepted by clinical experts in TA430.[139] The company further assumed that, in the absence of hazard ratios for GT5 and GT6, the GT4 hazard ratio would apply to GT5 and GT6.

ERG comment: Fibrosis progression was modelled using the equations by Thein et al. 2008,[158] which is the approach taken in TA253 and TA364.[177, 181] In Section 5.3, the ERG explored the scenario where the fibrosis progression was modelled using the equations from Grischchenko et al. 2009.[178]

TA430 did not distinguish between different non-cirrhotic fibrosis health states, and transition probabilities from fibrosis to CC were calculated from Kanwal et al. 2014.[2, 159]

Non-fibrosis progression

Non-fibrosis progression transition probabilities considered in the company's model include transition to the HCC health state from the corresponding "recovered" health state (i.e. SVR with history of CC) and the possible transitions between the CC, DCC and HCC health states, as depicted in Figure 5.1. Transition to HCC from the "recovered" health state was sourced from Cardoso et al. 2010,[182] while transitions between CC, DCC and HCC were taken from Fattovich et al. 1997.[160] These two sources

have been previously used in cost effectiveness analyses of HCV therapies in the UK.[153-155] However, the economic analyses in TA430 used Cardoso et al. 2010[182] to estimate the transition probabilities between CC, DCC and HCC. Both sources have been used previously in economic models in NICE submissions, and it has been concluded that both are generalisable to UK clinical practice and that the true value lies somewhere between.[176] Another deviation from TA430 is that the company's model considers a GT-specific hazard ratio which is applied to the transition probabilities from CC and DCC to HCC. These, as in the case of fibrosis progression transition probabilities, were sourced from Kanwal et al. 2014.[159]

Liver transplantation

The transition probability from DCC to LT was estimated from Siebert et al. 2003.[155, 183] This was done in TA430 and in other previous UK cost effectiveness models.[139, 153-155, 175] Unlike in TA430,[139] the company's model allows the transition from HCC to LT. The company argues that this is in line with current UK clinical practice.[184] The same transition probability used to model progression from DCC to LT was assumed for HCC to LT progression. This is in line with previous UK cost effectiveness models.[153, 155]

Liver-related mortality

Liver-related mortality risks for the DCC and HCC health states were obtained from Fattovich et al. 1997.[160] Mortality risks after liver transplantation are assumed to differ between the first and subsequent years after transplantation. For the year following liver transplantation (LT – first year) this was sourced from a survival analysis of UK registry data on liver transplantation, which was used in previous UK cost effectiveness studies.[154, 155, 175] For subsequent years, this was obtained from Bennett et al. 1997.[185]

ERG comment: The transition probabilities for DCC and HCC to liver death are in line with the models presented by Wright et al. (2006), Shepherd et al. (2007) and Hartwell et al. (2011).[153-155] The transition probability for HCC to liver death is the same as the one used in TA430.[139]

The value for the probability of death in the year following liver transplantation (LT – first year) has been used in UK cost effectiveness studies including Grieve et al. (2006), Shepherd et al. (2007), and Hartwell et al. (2011).[154, 155, 175] The transition probability from LT (subsequent year) to liver death was sourced from Bennett et al. (1997),[185] which was in line with the models presented in Shepherd et al. (2007) and Hartwell et al. (2011).[154, 155] In TA430, a single transition probability for liver transplant to death was used from Bennett et al (1997),[185] which is higher than those used in this model. However, the value used in this model is consistent with other models submitted recently to NICE such as TA365 and TA364.[156, 177, 186]

Note also that the transition probabilities used in the base-case do not change with age except for the transition probability to death from all causes and the age-dependent fibrosis stage-specific transition rates.

Summary of annual transition probabilities

Table 5.8: Annual transition probabilities

Variable	Base-case value	Source	TA430 value and reference [139]
GT1 fibrosis progression			
F0-F1	0.110	Equations from Thein et al. (2008)[158] and patient characteristics from TA364[177]	Model did not distinguish between non-cirrhotic fibrosis health states
F1-F2	0.088		
F2-F3	0.176		
F3-CC	0.143		See below in the table
GT-specific fibrosis progression multipliers			
GT2	0.68	Kanwal et al. (2014)[159] (adjusted hazard ratio)	F3-CC genotype-specific transition probabilities were calculated from Kanwal et al. (2014)[159]; GT1 0.0213, GT2 0.0165, GT3 0.0296, GT4 0.0202, GT5 0.0202, GT6 0.0202
GT3[a]	1.30		
GT4	0.94		
GT5	0.94	Assume same as GT4	
GT6	0.94		
Non-fibrosis disease progression			
SVR, history of CC (F4) to HCC	0.012	Cardoso et al. (2010)[182]	Same value and reference
CC to DCC	0.039	Fattovich et al. (1997)[160]	0.0438 Cardoso et al. (2010) [182]
CC to HCC; GT1	0.014		0.0631 Cardoso et al. (2010) [182]
DCC to HCC; GT1	0.014		0.0631 Cardoso et al. (2010) [182]
GT-specific non-fibrosis transition rate multipliers			
CC to HCC multiplier			
GT2	0.62	Kanwal et al. (2014)[159]	Not applied
GT3	1.44		
GT4	0.96		
GT5	0.96	Assumed same as GT4	
GT6	0.96		
DCC to HCC multiplier			
GT2	0.62	Assumed same as CC to HCC multiplier	Not applied
GT3	1.44		
GT4	0.96		
GT5	0.96		
GT6	0.96		
LT			
DCC to LT (first year)	0.020[b]	Siebert et al. (2003)[183]	0.022 Siebert et al. (2005)[187]

Variable	Base-case value	Source	TA430 value and reference [139]
HCC to LT (first year)	0.020[b]		Transition not allowed in model
Liver-related mortality			
DCC to liver death	0.130	Fattovich et al. (1997)[160]	0.24 EAP data (EASL 2016) [186]
LT first year to liver death	0.150	Grieve et al. (2006)[175]	0.2100 Bennett et al (1997) [185]
LT subsequent year to liver death	0.057	Bennett et al. (1997)[185]	
HCC to liver death	0.430	Fattovich et al. (1997) [160]	Same value and reference
Spontaneous remission from F0	0.000	Assumption (see Section B.3.2.2.3 in the CS)[2]	Same assumption
Background age- and gender-adjusted probability of death	Variable	ONS (2016)[173]	Same value and reference

Source: Table 75 in CS.[2]

[a] the inputs are based on Table 2 from Kanwal et al. (2014).[159] Note that there is a discrepancy in the publication for the GT3 fibrosis progression multiplier. In the introduction and the results section, the text mentions 1.31, but the results in Table 2 shows 1.30;

[b] For the transition probability form DCC to LT, Siebert et al. (2003)[183] actually use 0.022; Shepherd et al. (2011), and Wright et al. (2006) and Hartwell et al. (2011) use 0.02, so the model presented here has aligned with these other UK models.[153-155]

CC, compensated cirrhosis; DCC, decompensated cirrhosis; GT, genotype; HCC, hepatocellular carcinoma; LT, liver transplant; ONS, Office of National Statistics; SVR, sustained virologic response

5.2.7 Adverse events

Relevant adverse events (AEs) are included in the company's cost effectiveness model, which are assumed to impact both costs and health-related quality of life (HRQoL). However, the way AEs are implemented in the model differs for costs and HRQoL.

Costs associated to AEs are calculated in the model using AE rates observed in clinical trials. These AE rates are presented in Table 5.9 and Table 5.10 for treatment-naïve and treatment-experienced patients (and the corresponding genotype, treatment received and cirrhosis status), respectively. In particular, the following five AEs were included in the company's model: anaemia, depression, rash, Grade 3/4 neutropaenia and Grade 3/4 thrombocytopaenia. Other CHC-related AEs like nausea, vomiting, diarrhoea and pruritus were assumed to have a minor impact on the overall costs and therefore, these were not included in the company's model. Furthermore, the company assumed that, when AE rates were not reported separately for NC patients and CC patients, the same AE rates were applied for these two subgroups. Finally, for best supportive care (i.e. no treatment), the company assumed a 0% AE rate for all AEs.

Table 5.9: Inputs for AEs in TN patients using clinical trial data

Patient population (TN)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropaenia	Grade 3/4 thrombocy-topaenia	Reference
GT1	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ENDURANCE-1[39]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[47]
	OBV/PTV/RTV + DSV ± RBV	NC	3.84%	7.88%	0.00%	0.15%	0.15%	Pooled data from SAPPHIRE-I[80]and PEARL-IV[76]; weighted average with PEARL-III[76]
		CC	7.13%	10.96%	4.75%	1.19%	1.06%	TURQUOISE-II[77]
	EBR/GZR	NC	2.85%	0.00%	0.00%	0.32%	0.00%	C-EDGE TN[88]
		CC	2.85%	0.00%	0.00%	0.32%	0.00%	
	SOF/LDV	NC	0.93%	1.40%	0.00%	0.00%	0.00%	ION-3[93]
		CC	0.47%	4.88%	0.00%	0.47%	0.23%	ION-1[91]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[97]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
GT2	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 4[52]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[47]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.00%	0.00%	ASTRAL-2[98]
		CC	0.00%	0.00%	0.00%	0.00%	0.00%	

Patient population (TN)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropaenia	Grade 3/4 thrombocy-topaenia	Reference
	SOF + RBV	NC	4.24%	4.87%	3.18%	0.21%	0.00%	Pooled data from FISSION,[108] VALENCE[107] and ASTRAL-2[108]
		CC	4.24%	4.87%	3.18%	0.21%	0.00%	
	Peg-IFN + RBV	NC	11.52%	17.70%	13.99%	14.81%	7.41%	FISSION[109]
GT3	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ENDURANCE-3[25]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 3[52]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.26%	0.52%	Pooled data from ASTRAL-3[98] and POLARIS-3[188, 189]
		CC	0.00%	0.00%	0.00%	0.26%	0.52%	
	SOF + DCV ± RBV	NC	0.00%	0.75%	0.00%	0.00%	0.75%	Pooled data from ENDURANCE-3[25] and ALLY-3[112]
		CC	7.14%	0.00%	14.29%	0.00%	0.00%	A1444040[114]
	SOF + RBV	CC	0.00%	0.00%	0.19%	0.00%	0.76%	Pooled data from VALENCE[107]and ASTRAL-3[98]
	SOF + peg-IFN + RBV	CC	0.00%	19.80%	0.51%	15.74%	4.57%	BOSON[103]
GT4	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[52]

Patient population (TN)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropaenia	Grade 3/4 thrombocy-topaenia	Reference
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[47]
	OBV/PTV/RTV + RBV	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	PEARL-I (CSR)[190]
		CC[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AGATE-I (CSR)[191]
	EBR/GZR	NC	2.85%	0.00%	0.00%	0.32%	0.00%	C-EDGE TN[88]
		CC	2.85%	0.00%	0.00%	0.32%	0.00%	
	SOF/LDV	CC	0.00%	0.00%	0.00%	0.00%	4.55%	Study 1119[192]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[97]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
GT5	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[52]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[47]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[97]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	CC	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[110]
GT6	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[52]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[47]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[97]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	

Patient population (TN)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropaenia	Grade 3/4 thrombocy-topaenia	Reference
	SOF + peg-IFN + RBV	CC	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[110]

Source: Table 68 in CS.[2]

Note: For published references, if AEs were not reported (for example because only AEs affecting >5% of patients were reported), these were assumed to have a frequency of 0.

AEs, adverse events; CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TN, treatment-naïve; VEL, velpatasvir

Table 5.10: Inputs for AEs in TE patients using clinical trial data

Patient population (TE)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropaenia	Grade 3/4 thrombocy-topaenia	Reference
GT1	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ENDURANCE-1[39]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[47]
	OBV/PTV/RTV + DSV ± RBV	NC	3.67%	6.30%	0.00%	0.00%	0.00%	Weighted average of PEARL-II[75] and SAPPHIRE-II[81]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TURQUOISE-III (Feld et al. [2016][78] and CSR[193])
	EBR/GZR	NC	0.00%	0.00%	0.00%	0.00%	0.00%	C-EDGE TE[85]
		CC	0.00%	0.00%	0.00%	0.00%	0.00%	
	SOF/LDV	NC	0.00%	1.83%	0.00%	0.00%	0.92%	ION-2[92]
		CC	0.00%	1.83%	0.00%	0.00%	0.92%	
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[97]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
GT2	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 4[52]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[47]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.00%	0.00%	ASTRAL-2[98]
		CC	0.00%	0.00%	0.00%	0.00%	0.00%	

Patient population (TE)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropaenia	Grade 3/4 thrombocy-topaenia	Reference
	SOF + RBV	NC	3.45%	2.19%	2.19%	0.63%	0.63%	Pooled data from FUSION,[108] VALENCE[107] and ASTRAL-2[108]
		CC	3.45%	2.19%	2.19%	0.63%	0.63%	
GT3	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 3[52]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, pooled data from Parts 2 and 3[52]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.26%	0.52%	Pooled data from ASTRAL-3[98] and POLARIS-3[188, 189]
		CC	0.00%	0.00%	0.00%	0.26%	0.52%	
	SOF + DCV ± RBV	NC	0.00%	0.00%	0.00%	0.00%	1.32%	ALLY-3[112]
		CC	7.14%	0.00%	14.29%	0.00%	0.00%	A1444040[114]
	SOF + RBV	CC	0.00%	0.00%	0.19%	0.00%	0.76%	Pooled data from VALENCE[107]and ASTRAL-3[98]
	SOF + peg-IFN + RBV	CC	0.00%	19.80%	0.51%	15.74%	4.57%	BOSON[103]
GT4	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[52]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[47]
	OBV/PTV/RTV + RBV	NCc	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	PEARL-I(CSR)[190]

Patient population (TE)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropaenia	Grade 3/4 thrombocy-topaenia	Reference
		CCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AGATE-I (CSR)[191]
	EBR/GZR	NC	0.00%	0.00%	0.00%	0.00%	0.00%	C-EDGE TE[85]
		CC	0.00%	0.00%	0.00%	0.00%	0.00%	
	SOF/LDV	NC	0.00%	0.00%	0.00%	0.00%	4.55%	Study 1119[192]
		CC	0.00%	0.00%	0.00%	0.00%	4.55%	
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[97]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
GT5	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[52]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[47]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[97]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	CC	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[110]
GT6	G/P	NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SURVEYOR-II, Part 4[52]
		CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EXPEDITION-1[47]
	SOF/VEL	NC	0.00%	0.00%	0.00%	0.64%	0.16%	ASTRAL-1[97]
		CC	0.00%	0.00%	0.00%	0.64%	0.16%	
	SOF + peg-IFN + RBV	CC	20.80%	18.04%	9.48%	20.18%	0.31%	NEUTRINO[110]
Source: Table 69 in CS.[2]								

Patient population (TE)	Regimen	Cirrhosis status	Anaemia	Rash	Depression	Grade 3/4 neutropaenia	Grade 3/4 thrombocy-topaenia	Reference
Note: For published references, if AEs were not reported (for example because only AEs affecting >5% of patients were reported), these were assumed to have a frequency of 0. AEs, adverse events; CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; VEL, velpatasvir								

The company implemented the effect of AEs on HRQoL using treatment-related change in health utility (based on PROs). With this approach, the company aimed to capture the impact of all treatment-related AEs, not only those related to the AEs listed in Table 5.9 and Table 5.10. The operationalisation of HRQoL changes due to adverse events in the model are further described in Section 5.2.8 of this report.

ERG comment: The AE rates used in the model suffer from the same strong limitations as the SVR rates, i.e. the rates are based on single arms from various RCTs without any consideration of the comparability of these RCTs and for some subgroups the AE rates are based on very few patients.

As the impact of AEs is only explicitly incorporated for the costs outcome, the company argues that various AE that were previously included in TA430 (e.g. nausea, vomiting, diarrhoea and pruritus) could be excluded in the current model, due to their low associated costs. However, the validity of this reasoning depends not just on the associated costs, but also on the incidence of the AE. If low cost AEs occur in many patients, they may still have an impact on the outcomes. Thus, without an overview of all adverse events with their rates of occurrence, it is impossible to judge the validity of the current selection made by the company.

Note that the company has opted not to model the AE-related disutility explicitly, but instead has chosen to apply a treatment-related change in utility for all treatments for the duration of the treatment. Hence, the exact selection of AEs to include in the model can only impact the cost outcome, not the QALY outcome.

5.2.8 Health-related quality of life

As UK patients represented only a small percentage of the total enrolled patient sample in the various G/P studies, it was felt that the utilities collected from them would not be representative of the UK patients suffering with CHC. Furthermore, the trials for G/P did not enrol patients with DCC, HCC, or LTs. Thus, it was decided to use health state utilities identified from the literature, derived from UK patients. These utility values were all used in previous NICE submissions.[147, 156]

The base-case health utility values used for health states F0-F4 and SVR F0-F4 in the cost effectiveness model were derived from the study by Wright et al. 2006.[153] Utility values for more advanced liver disease (DCC, HCC, LT) and PLT were derived from Ratcliffe et al. 2002.[161] These values are presented in Table 5.11.

In a scenario analysis the company explored the impact of using trial-based utility values for health states F0-F3 and CC plus the SVR states associated with these five health states. It was considered more appropriate to use the literature-derived health-state utility values in the base-case for consistency with previous appraisals in chronic HCV.

In the CS, a utility increment of 0.05 for achieving SVR for patients with mild and moderate fibrosis and CC is assumed, occurring from the second cycle of the model onwards. This utility gain was based on data collected in the UK trial on mild HCV by Wright et al. 2006 and used to calculate the health state utility value for SVR with a history of mild (F0–F1) or moderate (F2–F3) fibrosis by Wright et al. 2006; the +0.05 increment was applied to the health state utility value for SVR with a history of CC by Shepherd et al. 2007 and Hartwell et al. 2011, and by previous NICE TAs.[147, 153-156] The SVR utility increment applied in this CS is different from that in TA430; in TA430 an SVR utility increment of +0.04 from Vera-Llonche et al. 2013 was applied.[194]

Table 5.11: Health state utilities used in the cost effectiveness model

Health state	Base-case value	Source	TA430 value and reference[1]
F0	0.77	Wright et al. 2006[153]	0.750 Wright et al. 2006[153]
F1	0.77		
F2	0.66		
F3	0.66		
CC	0.55		Same value and reference
SVR, history of mild fibrosis (F0, F1)	0.82	+0.05 added to mild fibrosis health state; Wright et al. 2006[153] and aligned with Shepherd et al. 2007 and Hartwell et al. 2011[154, 155]	0.790 (calculated from SVR utility increment of +0.04 from Vera-Llonche et al. 2013[194]
SVR, history of moderate fibrosis (F2, F3)	0.71	+0.05 added to moderate fibrosis health state[a]	
SVR, history of CC (F4)	0.60	+0.05 added to CC health state. Utility aligned with Shepherd et al. 2007 and Hartwell et al. 2011[154, 155]	0.590 (calculated; ERG: 0.55)
DCC	0.45	Ratcliffe et al. 2002[161]	Same value and reference
HCC	0.45		
LT (first year)	0.45		
LT (subsequent)	0.67		

Source: Table 77 in CS.[2]
[a]This value (0.71) is consistent with previous appraisals using a +0.05 utility increment for achieving SVR (e.g. TA413 and TA365),[147, 156] however, Hartwell et al. (2011), Shepherd et al.(2007) and Wright et al (2006) (referenced in these appraisals) used a value of 0.72.[153-155] The value of 0.71 has been used here to prioritise consistency with previous appraisals.
CC, compensated cirrhosis; DCC, decompensated cirrhosis; ERG, Evidence Review Group; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; SVR, sustained virologic response

Treatment-related health utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events. For comparator treatments, these (dis)utilities were derived from previous NICE submissions.[26, 66, 195, 196] For most treatments, a disutility was found ranging from -0.05 to -0.001. The mean overall utility change for EBR/GZR and SOF/LDV was 0 (i.e. no utility change), and for G/P, SOF/VEL, and OBV/PTV/RTV ± RBV (except for the TN NC subgroup) a utility increment was applied. The treatment-related health utility changes per the expected regimen duration were annualised (for example, a 12-week change would be reweighted by multiplying it by 12/52), and then applied to baseline utilities from Wright et al. 2006 in cycle 1 of the model,[153] in which treatment is received. For best supportive care (no treatment), the treatment-related change in health utility is 0. Annualised treatment-related health utility changes by treatment and patient population are summarised in Table 5.12. Finally, it should be noted that the methodology for calculating and applying treatment-related utilities in the CS is different from that of TA430.[139] In TA430 the manufacturer applied treatment-specific (multiplicative) utility increments for DAA therapies whilst utility decrements were applied for each AE. In the current company model no utility decrements are applied for individual AEs as this

may lead to double-counting, as the effect of treatment-related AEs on HRQoL would be captured in the treatment-related utility adjustment.

Table 5.12: Annualised treatment-related health utility changes by treatment and patient population

Regimen (duration in weeks) and patient population			Annualised change in treatment-related health utility
G/P (8)			[redacted]
G/P (12)			[redacted]
G/P (16)			[redacted]
OBV/PTV/RTV + DSV ± RBV	GT1, TN	NC (12)	[redacted]
		CC (12 or 24)	[redacted]
	GT1, TE	NC (12)	[redacted]
		CC (12)	[redacted]
OBV/PTV/RTV ± RBV[b] (12)	GT4, TN	NC	[redacted]
		CC	[redacted]
	GT4, TE	NC	[redacted]
		CC	[redacted]
EBR/GZR (12)[a]			0
SOF/LDV (12)			0
SOF/VEL (12)[b]			0.007
SOF + DCV ± RBV (12)	TN	NC	-0.002
		CC	-0.027
	TE	NC	-0.008
		CC	-0.027
SOF + peg-IFN + RBV (12)			-0.034
SOF + RBV (12)	GT2, TN	NC	-0.001
		CC	-0.001
	GT2, TE	NC	-0.006
		CC	-0.006
SOF + RBV (24)	GT3, TN	CC	-0.024
	GT3, TE	CC	-0.024
Peg-IFN + RBV (24)	GT2, TN	NC	-0.050

Source: Table 78 CS.[2]

[a]EQ-5D data was extracted from TA413 for C-EDGE TN.[147] It was assumed conservatively that the on-treatment change in health utility also applies to TE patients; [b]The ASTRAL trials did not collect EQ-5D data. The same treatment-related change in health utility as G/P (12 weeks) was assumed.

CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve VEL, velpatasvir

ERG comment: Using utilities derived from the literature[153] is consistent with the approach used in previous STAs.[25, 26, 195, 197] However, it also means that in this STA, as well as some of the previous STAs, utilities derived from RCTs have not been taken into account in the base-case. In the CS it is argued that UK patients represented only a small percentage of the total enrolled patient sample in the various G/P RCTs and that it was therefore felt that these utilities would not be representative of the UK patients suffering with CHC. A similar justification was given in the STA of EBR/GZR.[147] However, the ERG questions to what extend utility values published in 2006 (originating from EQ-5D questionnaires completed in 2002),[153] i.e. before the DAA-era, can be seen as representative of UK patients currently suffering with CHC.

As the RCT-based utilities are higher than those observed in Wright et al. 2006,[153] with smaller differences between F0-F1, F2-F3, and F4, and smaller differences between states with and without a SVR, it is relevant to assess the impact of changing the source of the health state utility values. This scenario analysis has been provided in the CS, and the results are presented in Section 5.3. There it can be seen that these RCT utility values lead to a higher number of QALYs per treatment, without really altering the conclusions regarding cost effectiveness.

From the RCT-based utility values as presented in Table 117 from the CS,[2] it can be seen that the difference in utility of a health state with or without SVR ranges from 0.025 to 0.029, substantially lower than the increment of 0.05 applied by the company.[153] This raises the question if the utility gain observed in Wright et al. 2006 can still be considered as a valid estimate.[153] The ERG therefore requested in their clarification letter (question B11) that the company would perform a scenario analysis with the SVR-gain set to 0, as an extreme scenario. [13] Although the company explained how to do such scenario analysis in the electronic model, they did not provide the results of that scenario analysis. Hence, the ERG ran the scenario and its results are presented in Section 5.3, showing only a minimal impact on the results.

The impact of receiving treatment on health-related quality of life was taken into account in the company model using utility increments and decrements. Note that these changes in utility were only applied while patients are on treatment but not through the whole model's time horizon. Conceptually, the ERG agrees with this approach as it takes into account both the impact of a quick response to treatment and the impact of adverse events. However, most of these adjustment estimates were based on the same studies as the estimates of SVR rates and AE rates, implying that all comments regarding those (see Section 4.6) apply here as well. Therefore, the ERG requested in their clarification letter (question B11) that the company would perform a (worst case) scenario analysis in which no utility adjustments would be applied.[13] However, the company opted not to provide the results of such analysis and instead only described which changes had to be made to run the analysis. In Section 5.3 the results of the scenario analysis as run by the ERG are presented.

5.2.9 Resources and costs

In the CS the costs for the clinical management of CHC are made up of two main components: 1) Health state costs and 2) treatment-related costs.

Health state costs capture the average medical costs in a specific health state. Costs include those associated with the management of progressive liver disease (in patients who do not respond to treatment) and with post-treatment surveillance following treatment cessation and achievement of SVR.

Treatment-related costs consist of drug acquisition costs multiplied by the mean treatment duration from trials, costs associated with on-treatment monitoring for response, and costs of treating adverse events to treatment.

5.2.9.1 Treatment-related costs

The CS presents a list price for G/P of £464.06 per day. List prices were also used for comparator products; Table 5.13 presents daily medication costs. Table 80 in the CS shows in detail how these costs per day have been derived from pack prices and treatment duration.[2]

Table 5.13: Treatment regime costs per day

Therapy	Regimen costs (per day, list price 2016 £)	Source	Comparison to TA430[1]
G/P (list price, indicative)	£464.06	AbbVie	Regimen costs were sourced from the BNF
OBV/PTV/RTV + DSV	£416.67	BNF 2016[198]	
OBV/PTV/RTV	£383.33		
EBR/GZR	£434.52		
SOF/LDV	£464.05		
SOF/VEL	£464.05		
SOF	£416.46		
DCV	£291.88		
RBV	£13.21		
IFN	£17.77		

Source: Table 79 in the CS.[2]
BNF, British National Formulary; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GZR, grazoprevir; IFN, pegylated interferon, LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; VEL, velpatasvir

The CS used information on the frequency of monitoring of patients (outpatient appointments, inpatient care, tests and investigations) whilst being treated with INF from Shepherd et al. 2007,[154] as was previously done in Hartwell et al. 2011[155] and in NICE submissions, including TA430.[156, 176] The values were adapted for DAA regimens. Costs were inflated to 2015/2016 values.[199] Estimations of monitoring costs per treatment duration are described in Table 5.14. Unlike TA430, the company did not stratify monitoring costs by cirrhosis status, and there are no monitoring costs for untreated patients.[139] These assumptions are consistent with the economic model submitted previously by the company for OBV/PTV/RTV ± DSV (TA365).[156]

Table 5.14: Monitoring costs during treatment

Duration therapy	Monitoring costs (2015/2016 £) (See also CS Table 81)	Source	Comparison to TA430
8 weeks – all-oral therapy	£303	Shepherd et al. (2007)[154] costs inflated to 2015/2016 values[199]	Monitoring costs were also based on Shepherd et al. 2007[154]
12 weeks – all-oral therapy	£420		
16 weeks – all-oral therapy	£477	Assume equal to 12 weeks monitoring costs + week 8 assessment (£57.52)	
24 weeks – all-oral therapy	£840	Assume proportional to 12 weeks	

Source: Table 79 in the CS.[2]

Frequencies of AEs for each treatment were previously described in Section 5.2.7. The company used data from Thorlund et al. 2012 to obtain resource use and unit cost for anaemia and rash (costs were inflated to 2015/2016 values).[199, 200] For depression, the company obtained assumptions used to inform the cost of treatment and monitoring from NICE GC 90: Depression in adults.[201] These inputs are in line with TA365 (OBV/PTV/RTV ± DSV).[156] Finally, the estimate of resource use for neutropaenia and thrombocytopaenia were based on NICE TA430.[139] A detailed breakdown of the resource use used to calculate the AE costs are described in Table 83 of the CS. Table 84 of the CS shows the differences between the AE costs in this model compared to TA430. A summary of the AE-related costs included in the economic model is presented in Table 5.15.

Table 5.15: Costs of treating adverse events

Treatment-related adverse event	costs (2015/2016 £)	Source	Comparison to TA430
Anaemia	£486	Thorlund et al. (2012)[200]	See Table 84 in the CS[2]
Rash	£160		
Depression	£490	NICE CG90 (2009)[201]	
Grade 3/4 neutropaenia	£1,334	TA430[139]	
Grade 3/4 thrombocytopenia	£1,902		
Source: Table 79 in the CS.[2]			

5.2.9.2 Health state unit costs and resource use

Health-state unit costs were derived from previous publications and inflated to 2014/15 values.[54, 60, 167] The same costs were applied to all genotypes and all subgroups.

Table 5.16 presents the cost estimates associated with each health state. The company used data from two studies, i.e. Hartwell et al. 2011 and Backx et al. 2014.[155, 202] The study by Backx et al. 2014 is a retrospective analysis of health resource usage and costs by patients in the East Midland region of the UK. It captured data for different disease states (e.g. fibrosis versus cirrhosis) and the data was evaluated according to response to treatment (SVR or non-SVR).[202] Therefore, values from this study were used in the CS for SVR health states and F2–F4 health states. In the CS it is conservatively assumed that all recovered patients require life-long monitoring post achieving an SVR, irrespective of their initial fibrosis stage.

In the absence of more recent or relevant sources, costs for F0 and F1 health states and those for more advanced liver disease (DCC, HCC, LT) were sourced by the company from Hartwell et al. 2011.[155] Costs were inflated to 2015/2016 values.[199] Compared to TA430, this model uses more recent inputs whenever possible from Backx et al. 2014,[202] in line with TA365,[156] whereas the majority of inputs for TA430 are from Wright et al. 2006.[153]

Table 5.16: Summary of health state costs

Health state	Costs per event (2015/2016 £)	Source	TA430 value and reference (2014/2015 £)
F0	£164	Hartwell et al. 2011[155]	£327 Calculation: 83%,17% split[a] Wright et al. 2006 [153] Mild: £189 (inflated) Moderate: £1,001 (inflated)
F1	£164		
F2	£609	Backx et al. 2014 [202]	
F3	£609		
CC	£945		£1,561 Wright et al. 2006 [153]

Health state	Costs per event (2015/2016 £)	Source	TA430 value and reference (2014/2015 £)
SVR, history of mild fibrosis(F0–F1)	£60	Backx et al. 2014 [202]	£246 Calculation: 83%,17% split[a] Grishchenko et al. 2009 [202] SVR, mild: £237 (inflated) SVR, moderate: £290 (inflated)
SVR, history of moderate fibrosis (F2–F3)	£60		
SVR, history of CC	£606		£513 Grishchenko et al. 2009 [178]
DCC	£12,670	Hartwell et al. 2011[155]	£12,510 Wright et al. 2006 [153]
HCC	£11,291		£11,147 Wright et al. 2006 [153]
LT (first year)	£51,108		1st year LT: £85,191; 1st year post LT 0-12 months: £28,067; subsequent year £4,194 (12-24 months). From Singh/Longworth et al. 2014 [203] split between post-liver transplant year 1 and year 2 cost based on Wright et al. 2006 [153]
LT (subsequent year)	£1,924		

Source: Table 82 in the CS.[2]
[a]Based on 83% F0-F2 (mild) and 17% F3 (moderate), derived from HCV TherapyWatch market research data.
AE, adverse event; CC, compensated cirrhosis; DCC, decompensated cirrhosis; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; SVR, sustained virologic response

ERG comment: Overall the ERG has few comments to make to the company's approach to including costs in the cost effectiveness analysis. It should be noted that Table 5.16 shows that for the health states F0, F1, DCC, HCC and LT estimates were obtained from a publication by Hartwell et al. 2011.[155] However, the paper by Hartwell et al. refers in turn to the study by Wright et al. 2006,[153] which was also used in TA430. Hence, though it appears that the current submission uses a different source for the cost estimates, in fact it uses the same as TA430 for F0, F1, DCC, HCC and LT.

In the health state cost estimates neither allied health care nor GP visits or home care have been included. Whilst it might be reasonable to assume that GP costs and allied health care costs will be relative small compared to hospital admissions and outpatient visits, this is less clear for home care, especially for patients with hepatocellular carcinoma or decompensated cirrhosis. Unfortunately, none of the cost studies identified by the manufacturer (CS Appendix I) reported these types of resource use, so no data was available for the ERG to add these.[16] However, the tornado diagrams reporting the DSA (CS appendix L.1.3) show that even when health state costs are changed by 50% this does not alter the conclusions, and for most subgroups the impact is extremely small.[16]

The determination of AE cost estimates is somewhat confusing to the ERG. For anaemia and rash the company favours the study by Thorlund et al. 2012,[200] in which experts were consulted, over the estimates from TA430, which were based on expert opinion. However, Thorlund also present an estimate for neutropaenia (of £25) which is only a small fraction of the cost estimate used both in this model and in TA430. A potential explanation could be that the estimate in Thorlund et al. refers to all grades of neutropaenia, whereas in the current model only grade 3 and 4 neutropaenia is included.

Observational data regarding resource use for adverse events would be needed to reduce the uncertainty that currently exists. However, from the lack of mentioning of AE costs in the tornado diagrams reporting the DSA (CS Appendix L.1.3) it can be deducted that even when adverse event costs are altered by 50%, they have an almost negligible impact on the results.[16]

5.2.10 Cost effectiveness results

Cost effectiveness results were presented incrementally including all relevant comparators for the different subgroups considered in the analyses. Subgroups were characterised by genotype (GT1 – GT6), treatment history (treatment-naïve or treatment-experienced) and cirrhosis status (non-cirrhotic or compensated cirrhosis). Furthermore, GT2 treatment-naïve patients were also subdivided by IFN-eligibility. This resulted in 26 subgroups in total as reported in Table 5.3 in Section 5.2.3.

Base-case incremental cost effectiveness analysis results

The results summarised in this section are sourced from Appendix B14 in the clarification responses.[17] These were provided by the company after it was discovered during the clarification phase (Question B14 in the clarification letter[17]), that the results reported in the CS did not match those obtained from the submitted economic model. In these analyses, list prices were used for G/P and all comparators.

Table 5.17 below provides an overview of the (list price) base-case cost effectiveness results per subgroup. In the CS, results often refer to both the £20,000 and £30,000 cost per QALY threshold, which might be leading to some confusion, given the vast amounts of results that need to be presented. Given the high level of uncertainty associated with the input parameters of the model, the ERG chose to describe the cost effectiveness results in this section based on the £20,000 threshold.

It was observed that, for non-cirrhotic patients, G/P was always cost effective except for the following two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. This is indicated with shaded cells in Table 5.17. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).

Table 5.17: G/P cost effectiveness per subgroup (based on list price deterministic full incremental results)

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	**Compensated cirrhosis**	**Non-cirrhotic**	**Compensated cirrhosis**
GT1	G/P cost effective 2nd lowest total costs highest QALYs (out of 6 interventions)	G/P cost effective 3rd lowest total costs highest QALYs (out of 6 interventions)	G/P cost effective 2nd lowest total costs highest QALYs (out of 6 interventions)	G/P not cost effective 4th lowest total costs 3rd highest QALYs (out of 6 interventions)
GT2	IFN-eligible: G/P not cost effective 3rd lowest total costs highest QALYs (out of 3 interventions)	IFN-eligible: G/P not cost effective 3rd lowest total costs highest QALYs (together with SOF/VEL) (out of 3 interventions)	G/P cost effective 2nd lowest total costs 2nd highest QALYs (out of 4 interventions)	G/P not cost effective 3rd lowest total costs highest QALYs (together with SOF/VEL) (out of 4 interventions)
	IFN-ineligible: G/P cost effective 2nd lowest total costs 2nd highest QALYs (out of 4 interventions)	IFN-ineligible: G/P not cost effective 4th lowest total costs highest QALYs (together with SOF/VEL) (out of 4 interventions)		
GT3	G/P cost effective 2nd lowest total costs 3rd highest QALYs (out of 4 interventions)	G/P cost effective lowest total costs G/P cost effective 2nd lowest total costs 2nd highest QALYs (out of 6 interventions)	G/P not cost effective 4th lowest total costs highest QALYs (out of 5 interventions)	G/P not cost effective 4th lowest total costs 2nd highest QALYs (out of 6 interventions)
GT4	G/P cost effective 2nd lowest total costs 4th highest QALYs (out of 5 interventions)	G/P not cost effective 5th lowest total costs highest QALYs (together with SOF/VEL) (out of 6 interventions)	G/P cost effective 2nd lowest total costs 2nd highest QALYs (out of 6 interventions)	G/P not cost effective 4th lowest total costs highest QALYs (together with SOF/VEL) (out of 6 interventions)
GT5	G/P cost effective	G/P not cost effective	G/P cost effective	G/P not cost effective

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
	2nd lowest total costs highest QALYs (out of 3 interventions)	3rd lowest total costs highest QALYs (together with SOF/VEL) (out of 4 interventions)	2nd lowest total costs 2nd highest QALYs (out of 3 interventions)	3rd lowest total costs highest QALYs (together with SOF/VEL) (out of 4 interventions)
GT6	G/P cost effective 2nd lowest total costs 2nd highest QALYs (out of 3 interventions)	G/P not cost effective 3rd lowest total costs highest QALYs (together with SOF/VEL) (out of 4 interventions)	G/P cost effective 2nd lowest total costs 2nd highest QALYs (out of 3 interventions)	G/P not cost effective 3rd lowest total costs highest QALYs (together with SOF/VEL) (out of 4 interventions)
Source: Electronic model.[204] GT = genotype; IFN = interferon; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); QALY = quality-adjusted life year; SOF = sofosbuvir; VEL = velpatasvir;				

A more detailed description of the cost effectiveness results per genotype is given below.

GT1 patients

The results of the base-case cost effectiveness analysis for GT1 non-cirrhotic patients showed that G/P dominated all its comparators, with the exception of no treatment, regardless of treatment history. Thus, for treatment-naïve patients G/P resulted in a total cost of £27,657, 16.30 QALYs and an ICER compared to no treatment of £2,239, while for treatment-experienced patients the total costs, total QALYs and ICER compared to no treatment were £27,604, 15.49 and £1,855, respectively. Therefore, at a threshold of £20,000 per QALY gained, G/P can be considered a cost effective treatment option for these subgroups.

For patients with compensated cirrhosis, different results were observed depending on the treatment history. Thus, for treatment-naïve patients G/P dominated all its comparators except EBR/GZR and no treatment, and resulted in a total cost of £55,208, 10.49 QALYs and an ICER compared to EBR/GZR of £10,633. For treatment-experienced patients G/P resulted in a total cost of £56,016 and 10.11 QALYs but it was dominated by SOF/VEL (produced more QALYs at lower costs), which presented an ICER of £6,144 compared to EBR/GZR.

GT2 patients

GT2 treatment-naïve patients were further subdivided based on IFN eligibility. For non-cirrhotic patients, G/P was cost effective depending on IFN eligibility. Thus, for IFN-eligible patients, G/P resulted in a total cost of £27,557, 16.30 QALYs and an ICER of £32,704 compared to PR. For IFN-ineligible patients G/P resulted in the same total costs and QALYs as in the IFN-eligible subgroup (the only difference between these two subgroups are the comparators included in the analysis) and an ICER of £4,433 compared to no treatment. For patients with compensated cirrhosis, the only difference between IFN-eligible and IFN-ineligible was that in the latter subgroup, SOF/RBV was added as an

additional comparator. However, SOF/RBV was extendedly dominated; thus, the results for G/P in GT2 treatment-naïve cirrhotic patients were the same regardless of IFN eligibility. In both cases G/P resulted in a total cost of £55,208 and 10.49 QALYs but it was dominated by SOF/VEL (produced same QALYs at lower costs), which presented an ICER of £3,498 compared to no treatment.

For GT2 treatment-experienced non-cirrhotic patients, G/P was the least expensive option, with the exception of no treatment, and resulted in a total cost of £28,745, 15.28 QALYs and an ICER compared to no treatment of £4,550. For patients with compensated cirrhosis, G/P resulted in a total cost of £54,832 and 10.25 QALYs but it was dominated by SOF/VEL (produced same QALYs at lower costs), which presented an ICER of £3,804 compared to no treatment.

GT3 patients

The results of the base-case cost effectiveness analysis for GT3 treatment-naïve patients showed that G/P was the least expensive option, with the exception of no treatment, regardless of cirrhosis status. Thus, for non-cirrhotic patients G/P resulted in a total cost of £28,619, 16.11 QALYs and an ICER compared to no treatment of £1,475, while for patients with compensated cirrhosis the total costs, total QALYs and ICER compared to no treatment were £55,604, 10.43 and £3,703, respectively.

For GT3 treatment-experienced, G/P was not cost effective, regardless of cirrhosis status. Thus, for non-cirrhotic patients G/P resulted in a total cost of £54,675, 15.33 QALYs and an ICER compared to SOF/PR of £157,141, while for patients with compensated cirrhosis the total costs, total QALYs and ICER compared to SOF/VEL were £69,411, 10.03 and £81,897, respectively.

GT4 patients

The results of the base-case cost effectiveness analysis for GT4 non-cirrhotic patients showed that G/P was the least expensive option, with the exception of no treatment, regardless of treatment history. Thus, for treatment-naïve patients G/P resulted in a total cost of £28,657, 16.06 QALYs and an ICER compared to no treatment of £3,033, while for treatment-experienced patients the total costs, total QALYs and ICER compared to no treatment were £27,271, 15.52 and £2,005, respectively.

For patients with compensated cirrhosis, G/P was dominated by SOF/VEL (produced same QALYs at lower costs) regardless treatment history. SOF/VEL was not cost effective in these subgroups. For treatment-naïve patients G/P resulted in a total cost of £55,208 and 10.49 QALYs, and for treatment-experienced patients these were £54,832 and 10.25, respectively.

GT5 patients

The results of the base-case cost effectiveness analysis for GT5 non-cirrhotic patients showed that G/P was the least expensive option, with the exception of no treatment, regardless of treatment history. Thus, for treatment-naïve patients G/P resulted in a total cost of £27,306, 16.33 QALYs and an ICER compared to no treatment of £2,417, while for treatment-experienced patients the results were the same as in GT4.

For patients with compensated cirrhosis, the results for G/P were the same as in GT4.

GT6 patients

The results of the base-case cost effectiveness analysis for GT6 non-cirrhotic patients showed that G/P was the least expensive option, with the exception of no treatment, regardless of treatment history. Thus, for treatment-naïve patients G/P resulted in a total cost of £29,501, 15.89 QALYs and an ICER compared to no treatment of £3,473, while for treatment-experienced patients the results were the same as in GT4.

For patients with compensated cirrhosis, the results for G/P were the same as in GT4.

5.2.11 Sensitivity analyses

Sensitivity analyses were undertaken in the 26 patient subgroups described in Section 5.2.3 of this report. Due to the large number of subgroups and comparators within each subgroup, the company judged it unfeasible to perform PSA/DSA for all treatment comparisons in all patient subgroups (cf. pp. 217 and 219 in the CS).[2] Thus, for each subgroup a comparison of G/P to a single comparator treatment was chosen. The comparator was selected as the one against which G/P had the lowest incremental net monetary benefit when valuing a QALY at £20,000. The comparators used by the company in the PSA/DSA are summarised per subgroup in Table 5.18.

Table 5.18: Comparators used for PSA/DSA analyses

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	SOF/LDV	EBR/GZR	OBV/PTV/RTV + DSV	SOF/VEL
GT2	IFN-eligible: peg-IFN + RBV IFN-ineligible: SOF + RBV	IFN-eligible: SOF/VEL IFN-ineligible: SOF/VEL	SOF/VEL	SOF/VEL
GT3	SOF/VEL	SOF/VEL	SOF + peg-IFN + RBV	SOF/VEL
GT4	OBV/PTV/RTV	OBV/PTV/RTV	OBV/PTV/RTV	OBV/PTV/RTV
GT5	SOF/VEL	SOF/VEL	SOF/VEL	SOF/VEL
GT6	SOF/VEL	SOF/VEL	SOF/VEL	SOF/VEL

Source: Table 113 in the CS.[2]
DSA = deterministic sensitivity analysis; DSV = dasabuvir; EBR = elbasvir; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; PSA = probabilistic sensitivity analysis; PTV = paritaprevir; peg-IFN = pegylated IFN; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; VEL = velpatasvir

ERG comment: The ERG considers that choosing a single comparator is methodologically incorrect and the interpretation of the results can be potentially misleading. In general, when more than two treatments have a positive cost effectiveness probability at a certain cost effectiveness threshold, restricting the analysis to two treatments only is likely to overestimate the cost effectiveness probability of the most cost effective treatment. Therefore, PSA with multiple comparators should have been performed.

Probabilistic sensitivity analysis

The company distinguished between treatment-specific and non-treatment specific input parameters. The first group included SVR rates, AE rates and treatment-related utility change. Treatment-specific input parameters were varied when possible using the 95% confidence intervals observed in the clinical trials. This was the case for SVR and AE rates, which were assumed to follow a Beta distribution, with the input parameters given by the trial subgroup sample size and percentage of patients achieving SVR or with an AE in that subgroup. SVR rates were summarised in Table 4.16 and AE rates in Table 5.9 and 5.10. Due to the lack of data, only for G/P was the treatment-related utility change (see Table 5.12)

included in the PSA, which was assumed to follow a Normal distribution. The non-treatment-specific input parameters included disease progression transition probabilities, health state costs and utilities and AE-related costs, and health utilities. A full list of the non-treatment-specific parameters with their corresponding lower and upper limits and assumed probability distributions can be found in Appendix 2. Other model input parameters (like treatment costs) were considered fixed and therefore not included in the PSA.

The company presented PSA results based on 500 model iterations. Results were reported as the probability that G/P is cost effective against the comparator chosen for each subgroup at £20,000 and £30,000 thresholds. As mentioned in Section 5.2.10, the ERG considered that reporting results for both thresholds might be confusing and given the high level of uncertainty associated with the input parameters of the model, only the results based on the £20,000 threshold are reported in this section. These probabilities can be seen in Table 5.19. For extensive PSA results, including cost effectiveness probabilities at the £30,000 threshold, we refer to Appendix 2. The model developed by the company can also produce scatter plots of the PSA outcomes on the cost effectiveness (CE) plane, a cost effectiveness acceptability curve (CEAC) and a cost effectiveness acceptability frontier (CEAF). However, these plots were not included in the CS.

Table 5.19: G/P cost effectiveness probability (%) at £20,000 threshold (against a single comparator)

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	99.4% (SOF/LDV)	60.8% (EBR/GZR)	100% (OBV/PTV/RTV + DSV)	12.0% (SOF/VEL)
GT2	IFN-eligible: 2.4% (peg-IFN + RBV)	IFN-eligible: 43.8% (SOF/VEL)	99.8% (SOF/VEL)	37.6% (SOF/VEL)
	IFN-ineligible: 100% (SOF + RBV)	IFN-ineligible: 43.8% (SOF/VEL)		
GT3	100% (SOF/VEL)	74.0% (SOF/VEL)	0.0% (SOF + peg-IFN + RBV)	0.2% (SOF/VEL)
GT4	67.6% (OBV/PTV/RTV)	14.4% (OBV/PTV/RTV)	100% (OBV/PTV/RTV)	1.6% (OBV/PTV/RTV)
GT5	100% (SOF/VEL)	48.6% (SOF/VEL)	100% (SOF/VEL)	37.6% (SOF/VEL)
GT6	70.4% (SOF/VEL)	46.6% (SOF/VEL)	100% (SOF/VEL)	45.4% (SOF/VEL)

Source: Table 53 in the CS.[2]
DSV = dasabuvir; EBR = elbasvir; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; PSA = probabilistic sensitivity analysis; PTV = paritaprevir; peg-IFN = pegylated IFN; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; VEL = velpatasvir

ERG comment: There are two major flaws in the PSA results presented by the company. The first one was considering a single comparator instead of all possible comparators in the analyses. The second one was not including a large number of SVR and AE rates in the PSA. The impact of these two issues

separately on the PSA results is explained below. As a consequence, the ERG considers the PSA results in the CS unreliable.

Despite being judged unfeasible by the company, the ERG was able to run all PSAs including all treatment comparisons in all patient subgroups. Detailed results of these PSAs are presented in Appendix 2. The ERG observed that for all subgroups consisting of non-cirrhotic patients, only G/P and the comparator chosen by the company for the PSA (see Table 5.18 above), had a positive cost effectiveness probability at the £20,000 threshold. Therefore, Table 5.19 reports the appropriate cost effectiveness probabilities for G/P at the £20,000 threshold for non-cirrhotic patients. However, this was not the case for the subgroups considering patients with compensated cirrhosis. In all of these 13 subgroups, there were at least two comparators with a positive cost effectiveness probability at the selected threshold. Table 5.20 shows the G/P cost effectiveness probability at the £20,000 threshold for patients with compensated cirrhosis when G/P is compared against only one comparator (as chosen by the company) and when G/P is compared with all the relevant comparators for each of the subgroups (Table 5.6). Whereas in most of the subgroups the difference in cost effectiveness probability can be deemed minor, for GT1, GT3 and GT4 treatment-naïve cirrhotic patients, the company overestimated the cost effectiveness probability of G/P by at least 10%.

Table 5.20: G/P cost effectiveness probability (%) at £20,000 threshold for patients with compensated cirrhosis in the company submission (against only one comparator) and with multiple comparators

HCV genotype	Treatment-naïve		Treatment-experienced	
	One comparator*	All comparators**	One comparator*	All comparators**
GT1	60.8%	50.2%	12.0%	9.0%
GT2	IFN-eligible*: 43.8%	IFN-eligible: 40.0%	37.6%	38.6%
	IFN-ineligible*: 43.8%	IFN-ineligible: 40.6%		
GT3	74.0%	61.6%	0.2%	1.0%
GT4	14.4%	0.6%	1.6%	1.8%
GT5	48.6%	45.0%	37.6%	40.0%
GT6	46.6%	46.0%	45.4%	42.4%

GT = genotype; IFN = interferon
*Comparators in Table 5.18; **Comparators in Table 5.6.
Note: shaded cells indicate a difference of at least 10% in the cost effectiveness probability of G/P vs. one or all relevant comparators for each subgroup.

It should be emphasised that, even when all relevant comparators are included in the PSA, the resulting uncertainty associated with the PSA results was considerably underestimated in certain subgroups. This was mainly caused by a programming error made by the company. The company modelled SVR and AE rates based on the actual number of observed events in the trials. While in principle this is methodologically correct, in many cases these observed rates were 100% or 0%, mostly due to a very low number of patients in a subgroup where all of them achieved SVR or none of them had AEs. In that situation, the estimated mean SVR or AE rate would be 100% or 0% but the estimated standard deviation would be zero. In order to account for the uncertainty around these extreme rates, some

adjustments need to be made in the model. In the company's electronic model, it is explicitly mentioned that when an SVR or AE rate "*was equal to 0% or 100%, a solution have been implemented to allow variation when running the PSA based on Briggs et al. More specifically, +1 was added to the denominator of all SVR rates and +1 was added in the numerator and denominator of all AE rates. Otherwise, PSA variation was not possible and was therefore assumed to remain at the same level*" (cf. electronic model – e.g. sheet 'Inputs – AbbVie GP' cell AD209).[204] However, this correction was not applied in the PSA performed by the company. Consequently, many of these rates were kept fixed in the analyses and were not included in the PSA. This produced invalid results since SVR or AE rates of 100% or 0%, respectively, were most often found in subgroups with a very limited number of observed patients (for one subgroup going as low as n=2) and these were now associated with low uncertainty whereas the opposite should be expected. The number of parameters not included in the PSA, and therefore, the uncertainty associated to its results, varies per subgroup. Table 5.21 shows the probability that G/P is cost effective against all relevant comparators chosen for each subgroup at a £20,000 threshold when all SVR and AE rates were included in the PSA and the difference in probability with respect to the PSA not including all relevant SVR and AE rates. Shaded cells indicate a difference of at least 10% absolute difference in the cost effectiveness probability of G/P against all relevant comparators for each subgroup. It is clear from Table 5.21 that the inclusion of parameter uncertainty around all SVR and AE rates can have a major impact on the G/P cost effectiveness probability for certain subgroups; but also that this impact can go in either direction (although more frequently it decreases the G/P cost effectiveness probability). This is especially striking for GT5 TN NC patients, for whom the company might have overestimated the cost effectiveness probability of G/P by 66 percent.

Table 5.21: G/P cost effectiveness probability (%) at £20,000 threshold against all comparators and including SVR and AE rates in PSA (difference with respect to PSA excluding SVR and AE rates in PSA)

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	100% (0%)	57.0% (+7%)	100% (0%)	3.4% (-6%)
GT2	IFN-eligible: 3.8% (+1%)	IFN-eligible: 56.2% (-16%)	99.8% (0%)	61.2% (+24%)
	IFN-ineligible: 100% (0%)	IFN-ineligible: 47.6% (+7%)		
GT3	100% (0%)	59.4% (-2%)	0.0% (0%)	1.0% (0%)
GT4	62.8% (-5%)	9.4% (+9%)	84.6% (-15%)	2.4% (+1%)
GT5	34.4% (-66%)	26.8% (-18%)	99.6% (0%)	20.0% (-20%)
GT6	41.2% (-29%)	46.0% (0%)	93.6% (-6%)	37.8% (-4%)

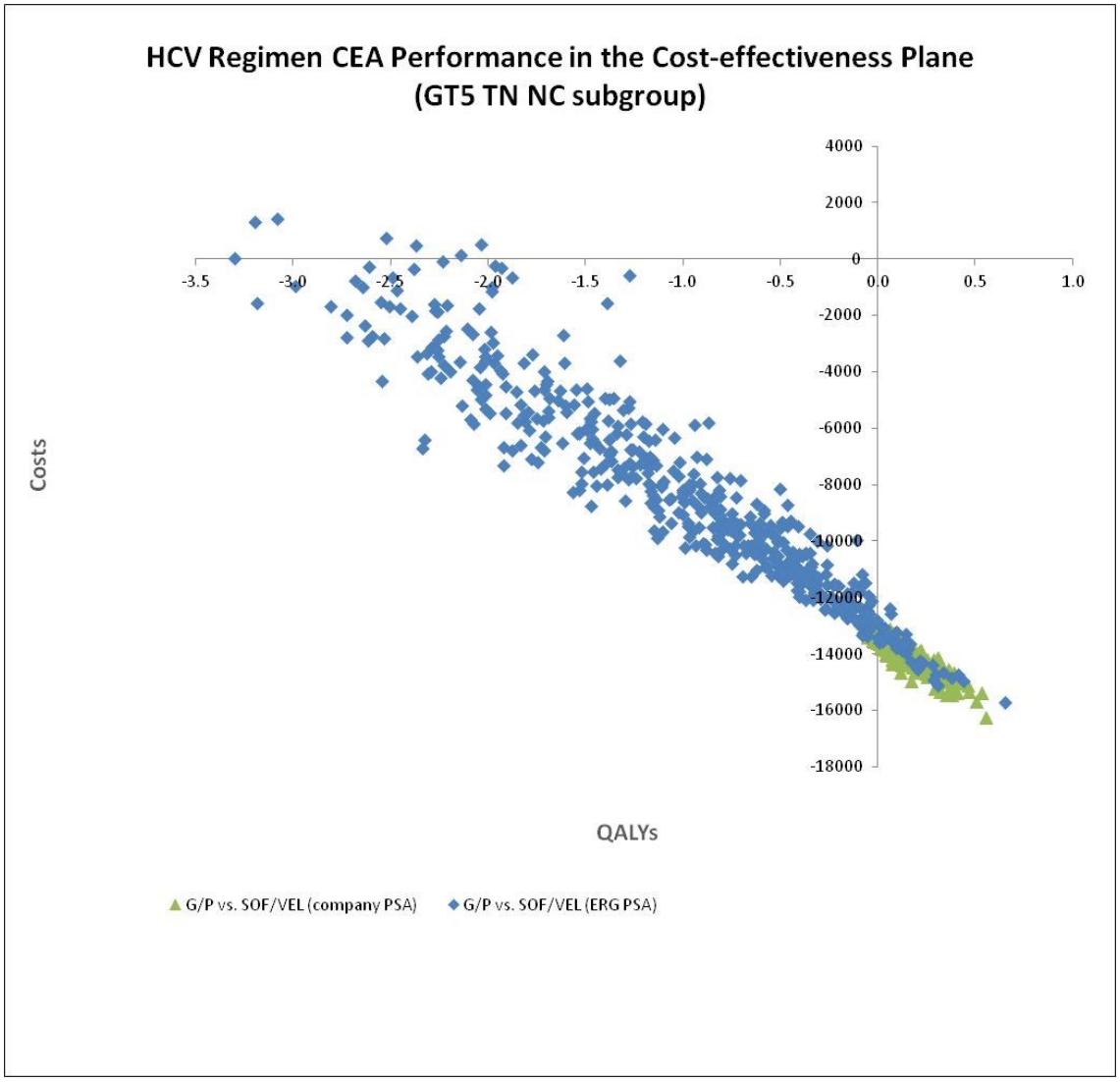
Source: Electronic model.[204]
GT = genotype; IFN = interferon; PSA = probabilistic sensitivity analysis

It should also be noted that a well-known feature of the cost effectiveness probability is that it only captures the probability of making the wrong decision, but not the consequences of making a wrong decision (as determined in a value of information analysis). For that reason, when reporting PSA results, it is considered insufficient to report only the cost effectiveness probability in any of its forms (table,

CEAC/CEAF) and a more detailed description of the PSA results should have been included in the CS (e.g. through plots of the PSA results on the CE-plane), especially for those subgroups for which high uncertainty was expected. This is illustrated below for GT5 TN NC and GT6 TN CC patients.

It was observed in Table 5.21 that the inclusion of all relevant SVR and AE rates reduced the cost effectiveness probability of G/P for GT5 TN NC patients by 66 percent. This can also be observed in Figure 5.2, where PSA results of G/P vs. SOF/VEL obtained with the company and ERG approaches were plotted on the cost effectiveness plane. This plot shows the great uncertainty (and skewness) of the ERG PSA results for this subgroup, which is intuitively credible when realising that the SVR rate of G/P was based on 2/2 patients, whereas the SVR rate for SOF/VEL was based on 28/29 patients.

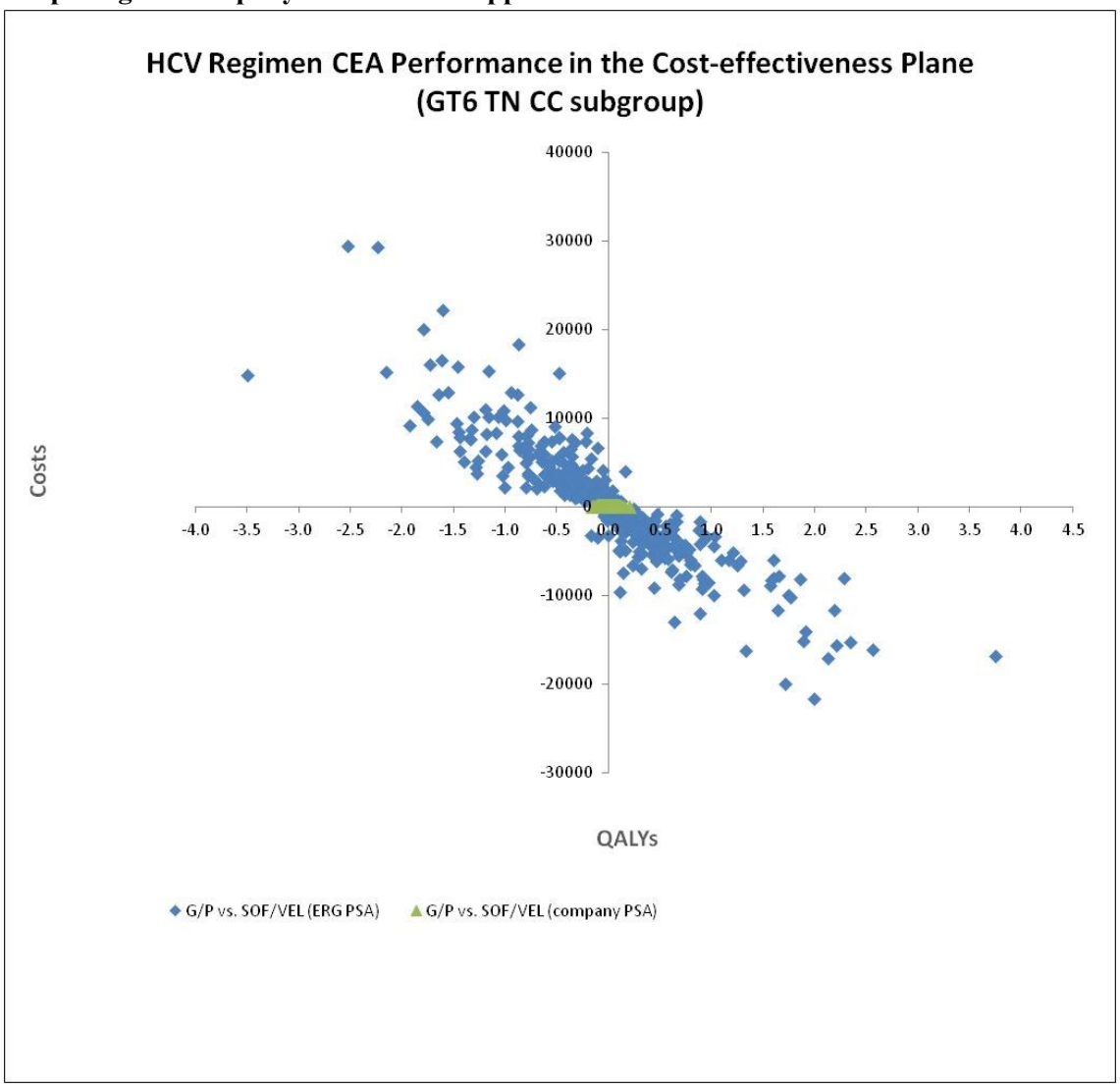
Figure 5.2: Cost effectiveness plane with G/P vs. SOF/VEL PSA results for GT5 TN NC patients comparing the company and the ERG approaches



Another interesting situation occurred for the GT6 TN CC subgroup. In Table 5.21, it was observed that the inclusion of all relevant SVR and AE rates did not change the cost effectiveness probability of G/P for these patients since it was 46% in both cases. However, by plotting the PSA results of G/P (SVR 6/6) vs. SOF/VEL (SVR 6/6) obtained with the company and ERG approaches on the cost effectiveness plane, it can be observed how different these two scenarios are. The plot in Figure 5.3 shows that although the number of PSA outcomes in the NW and SE quadrant might be comparable in both cases,

the ERG PSA outcomes are enormously scattered over these quadrants compared to the company's PSA outcomes. This scenario illustrates very clearly the main limitation of presenting cost effectiveness probabilities only. It shows two scenarios where these probabilities are comparable but the difference in decision uncertainty (e.g. in the consequences of making a wrong decision) is extremely large.

Figure 5.3: Cost effectiveness plane with G/P vs. SOF/VEL PSA results for GT6 TN CC patients comparing the company and the ERG approaches



Given the time constraints and the model complexity, the ERG could not produce detailed (corrected) PSA results for all subgroups. Nevertheless, it is considered that with the examples provided above, the major flaws in the PSA results presented by the company are properly explained. If it is judged that the analysis of uncertainty is a major concern for this submission, the PSA analyses should be repeated after tackling the issues presented in this section.

Deterministic sensitivity analysis

In response to the clarification letter,[17] the company presented tornado diagrams based on the INMB of G/P against one relevant comparator for all subgroups. These tornado diagrams were different from those presented in the original submission and they can also be found in Appendix 2. In Table 5.22 below, we indicate (based on the provided tornado diagrams) only those parameters for which the INMB changes its sign (from positive to negative or vice versa) since only these parameters are considered to

have the potential of reversing a cost effectiveness decision. For example, for the subgroup of GT1 non-cirrhotic treatment-naïve patients, the base-case INMB of G/P vs. SOF/LDV was positive. Therefore, in that case, G/P can be considered cost effective compared to SOF/LDV. The INMB remained positive for all the input parameters considered in the DSA except for the comparator SVR rates, which for high values resulted in a negative INMB. Thus, based on the DSA results for this subgroup, it can be concluded that only changes on the comparator SVR rates have the potential to make G/P not being considered cost effective. Overall, cost effectiveness based on INMB was not sensitive to changes on the input parameters considered in the DSA for 16 subgroups. For the other 10 subgroups, the INMB was most sensitive to changes in SVR rates for both intervention and comparator and for some utilities associated to the "recovered" health states.

Table 5.22: Input parameters which might influence the cost effectiveness results according to DSA (against comparator)

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	**Compensated cirrhosis**	**Non-cirrhotic**	**Compensated cirrhosis**
GT1	SVR rates comparator (SOF/LDV)	SVR rates comparator Utility – SVR history of severe cirrhosis (EBR/GZR)	None (OBV/PTV/RTV + DSV)	SVR rates intervention (SOF/VEL)
GT2	IFN-eligible: Utility – SVR history of mild fibrosis SVR rates comparator (peg-IFN + RBV)	IFN-eligible: None (SOF/VEL)	SVR rates intervention (SOF/VEL)	None (SOF/VEL)
	IFN-ineligible: None (SOF + RBV)	IFN-ineligible: None (SOF/VEL)		
GT3	None (SOF/VEL)	SVR rates comparator SVR rates intervention (SOF/VEL)	SVR rates comparator Utility – SVR history of mild fibrosis (SOF + peg-IFN + RBV)	None (SOF/VEL)
GT4	SVR rates intervention Utility – SVR history of mild fibrosis Utility – F1 (OBV/PTV/RTV)	SVR rates comparator (OBV/PTV/RTV)	None (OBV/PTV/RTV)	None (OBV/PTV/RTV)
GT5	None (SOF/VEL)	None (SOF/VEL)	None (SOF/VEL)	None (SOF/VEL)

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT6	SVR rates intervention Utility – SVR history of mild fibrosis Utility – F1 (SOF/VEL)	None (SOF/VEL)	None (SOF/VEL)	None (SOF/VEL)

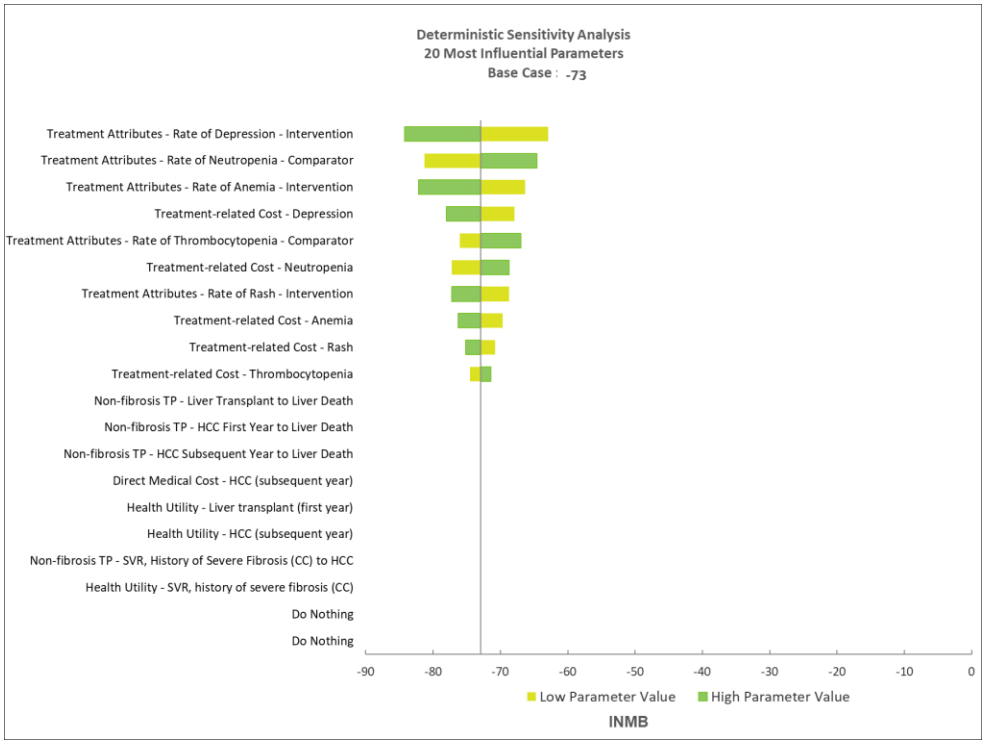
DSA = deterministic sensitivity analysis; DSV = dasabuvir; EBR = elbasvir; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; PSA = probabilistic sensitivity analysis; PTV = paritaprevir; peg-IFN = pegylated IFN; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; VEL = velpatasvir

Note: shaded cells indicate that the INMB of G/P vs. the corresponding comparator is positive and therefore, G/P can be considered cost effective in those cases.

ERG comment: Results were provided for G/P compared to a single comparator in each subgroup. Unlike PSAs, the ERG considers that this can be considered a pragmatic approach to DSA since an alternative methodology involving all comparators seems difficult to perform in practice. In any case, the DSA results should be interpreted with caution since the choice of a single comparator might produce biased results. If an indication of the degree of importance of individual parameters on the cost effectiveness results (including all comparators) is sought, then the expected value of partial perfect information seems a more reliable technique. This can be performed for example with the assistance of the SAVI tool.[205]

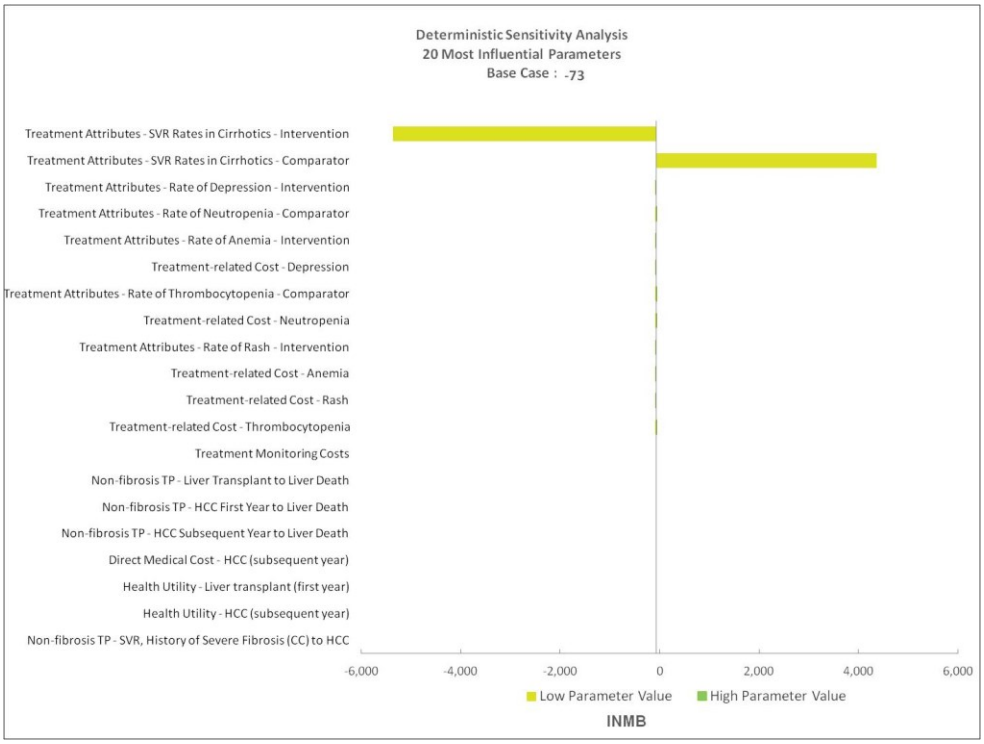
As explained in the PSA section, due to a programming error made by the company, many SVR and AE rates were not included in the DSA. This might produce misleading results since it can give the wrong impression that for subgroups based on a small number of patients the uncertainty is low, where the opposite should be expected. This is illustrated with Figure 5.4 and Figure 5.5. The first figure shows the tornado diagram provided by the company in response to the clarification letter for the subgroup of GT6 TE CC patients. Given the low number of patients in this subgroup used to estimate SVR rates (SVR rates for G/P based on five patients – cf. Table 4.16), one should expect high uncertainty associated to these parameters. However, these were not included in the DSA since they were assumed to be 100%. When lower limits for SVR rates were considered, Figure 5.5 shows that SVR rates are the parameters for which the INMB is most sensitive to changes. In fact, the difference in change in INMB with respect to the other parameters is so large that all the other parameters can be considered irrelevant. Given that these extreme rates often occur in subgroups with very few observations, it is not surprising that, when included in the DSA, these SVR rates are the parameters for which the model results are most sensitive. It should be noted though that this might have been a reporting error made by the company when presenting updated results after clarification. In all cases where a rate of 100% or 0% occurs, the model includes functionality to make sure that still a lower or upper boundary can be defined for the DSA. In Appendix L.1.3 of the CS, the tornado diagrams are based on this functionality. However, in the new set of results that was provided in their response to the clarification letter, the company did not invoke this functionality. Due to time constraints, the ERG could not correct this for all subgroups. The example shown here should be considered for illustrative purposes only and to indicate that the DSA results reported by the company (as presented in Appendix 2) can be unreliable for some subgroups.

Figure 5.4: Tornado diagram: GT6 TE CC, G/P vs. SOF/VEL



Source: response to clarification letter Appendix F.[17]

Figure 5.5: Tornado diagram including lower limits for SVR rates: GT6 TE CC, G/P vs. SOF/VEL



Source: Electronic model.[204]

5.2.12 Model validation and face validity check

In the CS (on page 222), it was mentioned that both technical/internal validation and external validation steps were undertaken.[2] In terms of technical validation, it was mentioned that two experienced, independent modellers reviewed the model structure and parameters and the software programme was checked and cleaned for potential programming errors by applying different routine tests. Furthermore, it was mentioned that the model's predictions were compared with the data that was used in the model, as part of the internal validation. The details and results of these validation efforts (technical/internal validation) were not reported.

As part of the external validation, the model's CC estimates for untreated mild-no fibrosis (F0) GT1 patients with specific baseline patient characteristics in line with Thein et al. 2008 were generated, and the 20-year post-infection CC rate from the model (21.3%) was compared with the cirrhosis estimates from other sources (Freeman et al. 2001, Alter and Seeff 2000, Seeff 2009 and Brady et al. 2007).[158, 206-209]

Freeman et al. 2001 reported a systematic review of 57 epidemiological studies.[207] The published studies were divided into four categories: liver clinic series, post-transfusion, blood donor and community-based studies. The mean prevalence of CC after 20 years of infection with HCV varied substantially among these four categories: 21.9% in the liver clinic series (N=492), 23.8 in the post-transfusion cohorts (N=72), 3.7% in the blood donor series (N=65) and 6.5% for the community based cohorts.

In Alter and Seeff 2000, the risk of progression to a severe clinical outcome at 20 years (defined as CC or HCC) was estimated to be approximately 20% from twelve studies examined adult patients with HCV.[208]

In a follow-up study by Seeff 2009, CC risk after 20 years from HCV infection was found to be 16%. This estimation varied substantially among different type of designs (18% for cross-sectional, 7% for retrospective-prospective studies, 18% for studies conducted in clinical setting and 7% for studies conducted in non-clinical setting).[209]

In Brady et al. 2007, in which an economic model was developed for the economic evaluation of PR for CHC treatment, a validation analysis was conducted and CC risk at 20 years was estimated to be around 19% for untreated patients.[206] This figure was in line with the review they conducted, which suggested a 20% risk of CC progression at 20 years for mild CHC patients.

ERG comment: In the CS, the details and the results of the technical and internal validation efforts were not reported. Upon ERG's request, more details on the model audit procedure was presented (Appendix B. 17 from the Response to the Clarification Letter).[17] Even though the description of the model auditing process gave a better overview of the technical validation efforts, the ERG considered that these efforts were mainly focused on the functionality of the drop-down menus or the VBA macros. In the description provided by the company, the types of the stress tests were lacking.

The ERG noticed several aspects of the model implementation that did not facilitate the technical validation of the model. For example, a number of hidden rows, which were active in the model's calculations, were controlled by a macro which made it unnecessarily complicated un-hiding them in order to check their values and references to other cells of the model. Activating an important functionality of the model as the one that includes estimates of lower or upper boundaries for SVR rates of 100% or AE rates of 0% was not straightforward. The PSA size is set within a macro but the sheet where this macro is recording the PSA outcomes is not prepared for a sample size larger than the default. While all these issues alone might be deemed as minor in other circumstances, given the large number

of subgroups included in the economic analyses, the adjustments that needs to be made for each of them (e.g. selecting the appropriate comparators) and the lack of time, the ERG considered that the aspects mentioned above could have been corrected in the model to facilitate its validation and to avoid an unnecessary burden on the ERG.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

In this section, the ERG conducted additional scenario analyses on the company base-case to explore the uncertainty around the assumptions taken in the company's base-case analysis. The ERG refrained from setting a preferred base-case, due to the concerns about the uncertainty surrounding SVR rates for the intervention and its comparators, which are caused by small sample sizes for some groups (e.g. n=2) as well as the method used to compare the effectiveness between treatments (naïve indirect comparison). Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses.

The following exploratory scenarios were conducted:

- No utility gain in SVR
- No treatment effect in utility
- Age based utility decrement
- Alternative transition probability inputs for fibrosis states
- Non-zero re-infection rates

5.3.1 Scenario-1: No utility gain in SVR

In this scenario, it was assumed that after SVR, there is no additional gain in health utility, whereas in the base-case a utility gain of 0.05 was assumed. In this scenario, it was assumed that after SVR, there is no utility gain, whilst in the base-case a utility gain of 0.05 was assumed. The removal of this utility gain has no impact on the ranking of G/P regarding cost effectiveness (yes or no in a subgroup), total costs, and total QALYs; these remain the same as presented in Table 5.17.

5.3.2 Scenario-2: No treatment specific health utility change

In this scenario, it was assumed that there is no treatment-related health utility change whilst on treatment. In the base-case, the values given in Table 5.12 were applied. Removing these utility adjustments had only an impact on the QALY ranking for GT4, GT5 and GT6, for TE NC patients. It had no impact on the ranking of G/P regarding cost effectiveness and total costs.

Table 5.23: G/P cost effectiveness per subgroup, without a treatment-related utility adjustment (based on list price deterministic full incremental results)

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	same as Table 5.17	same as Table 5.17	same as Table 5.17	same as Table 5.17
GT2	IFN-ineligible: same as Table 5.17	IFN-eligible: same as Table 5.17	same as Table 5.17	same as Table 5.17
	IFN-ineligible: same as Table 5.17	IFN-ineligible: same as Table 5.17		
GT3	same as Table 5.17	same as Table 5.17	same as Table 5.17	same as Table 5.17
GT4	same as Table 5.17	same as Table 5.17	G/P cost effective 2nd lowest total costs	G/P not cost effective

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
			highest QALYs (together with SOF/VEL, EBR/GZR and OBV/PTV/RTV + DSV ± RBV)	4th lowest total costs highest QALYs (together with SOF/VEL and *LDV/SOF*)
GT5	same as Table 5.17	same as Table 5.17	G/P cost effective 2nd lowest total costs *highest QALYs (together with SOF/VEL)*	same as Table 5.17
GT6	same as Table 5.17	same as Table 5.17	G/P cost effective 2nd lowest total costs *highest QALYs (together with SOF/VEL)*	same as Table 5.17

Source: Electronic model.[204]
GT = genotype; IFN = interferon; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); QALY = quality-adjusted life year; SOF = sofosbuvir; VEL = velpatasvir; DSV = dasabuvir; EBR = elbasvir; GZR = grazoprevir; LDV = ledipasvir; OBV = ombitasvir; PTV = paritaprevir; RTV = ritonavir; RBV = ribavirin;

5.3.3 Scenario-3: Age-based utility decrement

In this scenario, age based utility decrements derived from Ara and Brazier 2010[210] were applied. In the base-case, no age based utility decrements were applied. The addition of these age based utility decrements has no impact on the ranking of G/P regarding cost effectiveness, total costs, and total QALYs; these remain the same as presented in Table 5.17.

5.3.4 Scenario-4: Alternative transition probabilities for the fibrosis states

In this scenario, alternative transition probabilities from Grischenko et al. 2009 were applied for the transitions between the fibrosis states.[178] In the base-case transition probabilities from Thein et al. 2008 were used.[158] When compared with the base-case results, the addition of these alternative transition probabilities has no impact on the ranking of G/P regarding cost effectiveness, total costs, and total QALYs; these remain the same as presented in Table 5.17.

5.3.5 Scenario-5: Non-zero re-infection rates

In this scenario, alternative probabilities for re-infection from SVR states were incorporated. The re-infection probability estimate of 0.0033 from Simmons et al. 2016[211] was assumed. In the base-case re-infection probability was assumed to be zero. The addition of these re-infection probabilities has no impact on the ranking of G/P regarding cost effectiveness, total costs, and total QALYs; these remain the same as presented in Table 5.17.

5.4 Conclusions of the cost effectiveness section

The ERG considered that the economic model described in the CS meets the NICE reference case to a reasonable extent. While the economic model is in line with the decision problem formulated by the company, it is only partially in line with the scope. Intervention and comparators included in the company's economic analysis were also included in the scope. However, other relevant comparators listed in the NICE scope [1) DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE); 2) IFN with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients); 3) SOF in combination with RBV, with or without IFN (for specific people with GT1 and GT4; as recommended by NICE)] were not included in the company's cost effectiveness analysis because, according to the company, these are not used in current NHS practice. Furthermore, despite being included in the scope, the company did not perform subgroup analyses for patients who are co-infected with HIV and post-liver transplantation. The subgroup of patients who are intolerant to or ineligible for interferon treatment were only considered for GT2 TN patients.

The ERG assessment indicated that the model was presented and reported appropriately except for the sensitivity analyses. The company developed a de novo cost effectiveness model to assess the cost effectiveness of G/P compared to nine different comparators: BSC-watchful waiting, DCV/SOF, DCV/SOF/RBV, EBR/GZR, LDV/SOF, OBV/PTV/DSV+DSV ± RBV, PR, SOF/PR, SOF/RBV and SOF/VEL.

The cost effectiveness analyses performed by the company are in line with previous STAs for HCV treatments. The population considered in the cost effectiveness analyses was sub-divided into 26 different subgroups, where patients were stratified by genotypes (GT1, GT2, GT3, GT4, GT5 and GT6), treatment experience (treatment-naïve and treatment-experienced patients), cirrhosis status (cirrhotic and non-cirrhotic patients) and IFN-eligibility (only for GT2 TN patients).

The cost effectiveness model developed for this submission was a Markov model which consists of 13 health states. Non-cirrhotic patients start from states F0-F3, and cirrhotic patients start from F4. All treatment related outcomes (achieving SVR, treatment related adverse events and discontinuation) occur within the first year of the model. Patients who do not achieve SVR are at risk of progressing to more severe states. Patients who reached F4 can progress to DC and HCC states, which may lead to liver transplantation and liver related death. Liver transplantation state was divided into two categories (first year and later years).

The model uses health state based utilities from the literature (utilities that were used in Wright et al. 2006[153] and Ratcliffe et al. 2002[161]) in line with previous STAs for HCV treatments. A utility increment of 0.05 due to SVR is applied based on Shepherd et al. 2007[154] and Hartwell et al. 2011[155]. Treatment-related health utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events.

List prices were used as treatment costs for G/P and the comparator treatments in the cost effectiveness analysis. Health state costs (disease management costs based on disease stage) and other costs for adverse events were based on literature, expert opinion, UK reference costs and previous appraisals for HCV (especially TA430).

It should be noted that while the current model structure does not allow for sequential treatments, in clinical practice, patients who do not achieve SVR (who do not respond to the therapy or discontinue due to adverse events) or who were re-infected after SVR may receive further lines of treatments.

Onward transmission was not included in the economic model. Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework. Similarly, the company assumed a zero-reinfection probability after reaching SVR and assumed that no natural recovery takes place, despite contrary evidence reported in the clinical literature.

Treatment effectiveness was modelled as the probability of achieving SVR. Other treatment-specific parameters included adverse event rates, treatment duration, and treatment-related utility adjustments. All these parameter estimates were based on naïve indirect comparison of clinical trials assessing the efficacy of G/P and its comparators in the relevant subgroups. The ERG has concerns on the plausibility of this approach, which is not in line with the evidence synthesis best practices and susceptible to bias. Furthermore, some of the SVR rates were derived from very small sample sizes or the effectiveness in a subgroup was assumed to hold in another subgroup. Since SVR probability is the main driver of costs and effectiveness, all these assumptions create a substantial uncertainty on the cost effectiveness of G/P.

Furthermore, it was not clear to the ERG why age-dependent transition probabilities were not updated every year.

The health state utilities from RCTs could have been used by the company in their cost effectiveness analysis instead of the utilities from the literature. The ERG questions to what extend utility values published in 2006 (originating from EQ-5D questionnaires completed in 2002),[153] i.e. before the DAA-era, can be seen as representative of UK patients currently suffering with CHC. Similarly, the RCT-based utility values show a difference in utility with or without SVR ranging from 0.025 to 0.029, substantially lower than the increment of 0.05 applied by the company based on Wright et al. 2006[153] thus raising doubt about the validity of the latter value.

The impact of receiving treatment on QoL during treatment was taken into account in the company model using utility increments and decrements. However, most of these adjustment estimates were based on the same studies as the estimates of SVR rates and AE rates, implying that all comments regarding those (see Section 4.6) apply here as well.

The ERG was unsure about the completeness of the health state cost estimates used in the model, as items such as GP visits and home care costs are not included.

The base-case cost effectiveness results showed that, for non-cirrhotic patients, G/P was always cost effective except for the following two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).

Additionally, the company conducted probabilistic, deterministic and scenario analyses. Probabilistic results were reported as the probability that G/P is cost effective against one single comparator for each

subgroup at £20,000 and £30,000 thresholds. The comparator was selected as the one against which G/P had the lowest incremental net monetary benefit when valuing a QALY at £20,000. The result of the deterministic sensitivity analyses showed that in general the ICER was most sensitive to changes in SVR rates. Two scenario analyses conducted by the company first demonstrated how the cost effectiveness of G/P might change after the CMU price agreement (when comparators from other companies were based on list prices). Second, it was shown that using trial based utilities increased total QALY estimates compared to the base-case when literature based utilities were used as input.

There are two major flaws in the probabilistic analyses presented by the company. The first one was considering a single comparator instead of all possible comparators in the analyses. The second one was not including a large number of SVR and AE rates (those that were 100% or 0%) in the probabilistic analyses. As a consequence, the ERG considers the PSA results in the CS unreliable. Given the time constraints and the model complexity, the ERG could not produce detailed (corrected) PSA results for all subgroups. If it is judged that the analysis of uncertainty is a major concern for this submission, the PSA analyses should be repeated after taking care of the issues discussed in this report.

The ERG is concerned over the validation status of the cost effectiveness analysis by the company. The tests conducted for the technical verification of the model were not presented and the only validation effort was the external validation of the model estimates of the cirrhosis risk in 20 years from the clinical literature. The company submission would also benefit from a more transparent electronic model.

The ERG did not present an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses. In the scenario analyses assumptions surrounding the utility gain due to SVR, impact of the treatment on utility, impact of age on utility were challenged. In addition alternative inputs for transition probabilities in between fibrosis stages and re-infection rates were explored. Even though these scenarios changed the total costs and/or total QALYs estimates, the impact on incremental results were minimal. The cost effectiveness of G/P in each subgroup did not change, hence the cost effectiveness results of the base-case seem to be robust to changes in utility and treatment unrelated clinical model inputs.

In addition, the exploratory PSA analyses conducted by the ERG showed that that the inclusion of parameter uncertainty around all SVR and AE rates (which was not included in the company's base-case) can have a major impact on the G/P cost effectiveness probability for certain subgroups; but also that this impact can go in either direction (although more frequently it decreases the G/P cost effectiveness probability). This was especially striking for GT5 TN NC patients, for whom the company might have overestimated the cost effectiveness probability of G/P by 66 percent. Furthermore, the ERG showed that the PSA outcomes were enormously scattered over the CE plane quadrants for a number of subgroups and illustrated the main limitation of presenting cost effectiveness probabilities only (as in the CS).

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG has not presented an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses in Section 5.3.

7. OVERALL CONCLUSIONS

7.1 Statement of principal findings

Eighty-one publications (reporting on 79 studies) were identified as meeting the eligibility criteria. Fourteen of these publications, representing seven studies, involved G/P. In addition, information on four further clinical studies of G/P in patients with CHC are included in the company submission. These studies were conducted in special populations of patients with HIV co-infection, renal impairment, failure on prior DAAs and a post-transplant population. Finally, the company mentions two trials in Japanese patients with CHC: CERTAIN-1 and CERTAIN-2. These trials are only minimally discussed in the CS and not included in the economic model because "*these two trials were conducted entirely in Japanese patients*" which "*precludes their generalisability to the UK patient population and subsequently their use in the economic model*", according to the company.[2] Apart from these two trials in Japanese patients, none of the included studies presented comparative data for the licensed treatment duration of G/P with any of the comparators.

The G/P studies included patients with all genotypes; treatment-naïve and experienced patient populations; and patients with 'no cirrhosis and compensated cirrhosis'.

When split by cirrhosis status and previous treatment (naïve or experienced), SVR rates were consistently above 90% for all genotypes, except for GT2/TE/NC ([redacted] in SURVEYOR-II, Part 4; but [redacted] in SURVEYOR-II, Parts 1 and 2), GT3/TE/CC ([redacted] in SURVEYOR-II, Part 2; but [redacted] in SURVEYOR-II, Part 3) and GT6/TN/NC ([redacted] in SURVEYOR-II, Part 4).

Health-related quality of life (HRQoL) questionnaires indicated [redacted] In studies without a comparator, many treatment arms [redacted]

According to the company, G/P has a favourable safety profile that was similar to placebo and SOF/DCV, and that was similar across durations of eight, 12, and 16 weeks. G/P was well tolerated across a broad and diverse population of patients, including patients with CC, HIV co-infection, and CKD Stage 4/5. Common study adverse drug reactions (ADRs) occurring in ≥5% of patients were headache, fatigue, and nausea. Adverse drug reactions were mostly Grade 1 (mild) in severity. Serious ADRs and ADRs leading to premature study drug discontinuation were rare (≤0.1%).

The results of the company's base-case showed that, for non-cirrhotic patients, G/P was always cost effective except for the following two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above

cost effectiveness threshold). Probabilistic results were reported by the company as the probability that G/P is cost effective against one single comparator for each subgroup at £20,000 and £30,000 thresholds. However, the ERG showed that including all comparators in the PSA could substantially alter the probability that G/P would be cost effective. The result of the deterministic sensitivity analyses showed that in general the ICER was most sensitive to changes in SVR rates. Two scenario analyses conducted by the company first demonstrated how the cost effectiveness of G/P might change after the CMU price agreement (when comparators from other companies were based on list prices). Second, it was shown that using trial based utilities increased total QALY estimates compared to the base-case when literature based utilities were used as input, without really altering the conclusions from the base-case analyses.

The ERG did not present an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses.

In the scenario analyses assumptions surrounding the utility gain due to SVR, impact of the treatment on utility, impact of age on utility were challenged. In addition alternative inputs for transition probabilities in between fibrosis stages and re-infection rates were explored. Even though these scenarios changed the total costs and/or total QALYs estimates, the impact on incremental results were minimal. The cost effectiveness of G/P in each subgroup did not change, hence the cost effectiveness results of the base-case seem to be robust to changes in utility and treatment unrelated clinical model inputs.

The exploratory PSA analyses conducted by the ERG showed that that the inclusion of parameter uncertainty around all SVR and AE rates (which was not included in the company's base-case whenever rates were 100% or 0%) can have a major impact on the G/P cost effectiveness probability for certain subgroups; but also that this impact can go in either direction (although more frequently it decreases the G/P cost effectiveness probability). This was especially striking for GT5 TN NC patients, for whom the company might have overestimated the cost effectiveness probability of G/P by 66 percent. Furthermore, the ERG showed that the PSA outcomes were enormously scattered over the CE plane quadrants for a number of subgroups and illustrated the main limitation of presenting cost effectiveness probabilities only (as in the CS).

7.2 Strengths and limitations of the assessment

The conclusion from the G/P studies is that G/P has high SVR rates in all genotypes. In addition, G/P has a relatively favourable safety and tolerability profile. However, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each group. Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators relies on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. In most cases the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.

The main strength of the CS is that the structure of the economic model is in line with previous models presented in appraisals for HCV submitted to NICE and therefore, it reflects the main aspects of the chronic HCV disease. The model also includes relevant adverse events, utilities and costs.

The main limitation of the CS is that, since the key parameters in the cost effectiveness analyses (SVR rates) were based on the treatment effectiveness data, all health economic analyses suffered from the uncertainty of clinical effectiveness (comparative SVR rates). Furthermore, both probabilistic and deterministic sensitivity analyses presented by the company were performed incorrectly. As a consequence, the sensitivity analysis results in the CS are unreliable. If it is judged that the analysis of uncertainty is a major concern for this submission, these analyses should be repeated after tackling the issues discussed in this report. The company submission would also benefit from a more transparent electronic model.

7.3 Suggested research priorities

Head to head trials of direct-acting antivirals (DAAs) are warranted in patients with HCV.

Clinical and cost effectiveness for the treatment sequences in HCV should be explored. Furthermore, subgroup analyses for the cost effectiveness of G/P in interferon ineligible/intolerant populations and patients co-infected with HIV should be conducted. The population level effects of new DAA treatments should be explored via a dynamical model. In the current landscape, a MTA of non-DAA, partly DAA and all-DAA treatment regimens would guide the decision makers and benefit the efficient use of resources of the UK healthcare system. Non-RCT based utility studies for HCV health states would help to understand the difference between the estimates in Wright et al. 2006[153] and utilities directly obtained from the DAA RCTs.

8. REFERENCES

[1] European Medicines Agency. *EPAR summary for the public. Maviret: glecaprevier/pibrentasvir [Internet]*. London: EMA, 2017 [accessed 7.9.17] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004430/WC500233680.pdf

[2] AbbVie. *Glecaprevir/pibrentasvir for treating chronic hepatitis c: submission to National Institute for Health and Care Excellence. Single technology appraisal (STA)*. Maidenhead: AbbVie, 2017. 238p.

[3] Public Health England. *Hepatitis C in the UK: 2015 report [Internet]*. London: Public Health England, 2015 [accessed 8.8.17]. 110p. Available from: http://www.hcvaction.org.uk/sites/default/files/resources/Hepatitis%20C%20in%20the%20UK%202015%20report.pdf

[4] Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. *Int J Med Sci* 2006;3(2):47-52.

[5] Public Health England. *Hepatitis C in England: 2017 report. Working to eliminate hepatitis C as a major public health threat [Internet]*. London: Public Health England, 2017 [accessed 8.8.17]. 57p. Available from: http://www.hcvaction.org.uk/sites/default/files/resources/hepatitis_c_in_england_2017_report.pdf

[6] Negro F, Forton D, Craxi A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. *Gastroenterology* 2015;149(6):1345-60.

[7] Westbrook RH, Dusheiko G. Natural history of hepatitis C. *J Hepatol* 2014;61(1 Suppl):S58-68.

[8] The Hepatitis C Trust. *The uncomfortable truth. Hepatitis C in England: the state of the nation [Internet]*. London: The Hepatitis C Trust, 2013 [accessed 8.8.17] Available from: http://www.hcvaction.org.uk/sites/default/files/resources/The%20Uncomfortable%20Truth.pdf

[9] European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. *J Hepatol* 2017;66(1):153-94.

[10] European Medicines Agency. *Summary of opinion (initial authorisation). Maviret: glecaprevier / pibrentasvir [Internet]*. London: EMA, 2017 [accessed 24.8.17] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004430/WC500229790.pdf

[11] European Medicines Agency. *Summary of product characteristics. Glecaprevir & pibrentasvir (Maviret): draft SPC_26-06-2017*. Leatherhead: EMA, 2017

[12] National Institute for Health and Care Excellence. *Final scope for the single technology appraisal of glecaprevir-pibrentasvir for treating chronic hepatitis C [Internet]*. Manchester: NICE, 2017 [accessed 24.8.17] Available from: https://www.nice.org.uk/guidance/gid-ta10169/documents/final-scope

[13] National Institute for Health and Care Excellence. *Glecaprevir/pibrentasvir for treating chronic hepatitis C [ID1085]. Clarification letter*. London: NICE, 2017

[14] Canadian Agency for Drugs and Technologies in Health. *CADTH peer review checklist for search strategies [Internet]*. Ottawa: CADTH, 2013 [accessed 17.7.13]. 3p. Available from: http://www.cadth.ca/en/resources/finding-evidence-is

[15] National Institute for Health and Care Excellence. *Single Technology Appraisal: specification for manufacturer/sponsor submission of evidence [Internet]*. London: NICE, 2012 [accessed 22.9.17]. 76p. Available from: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Specification-for-manufacturer-sponsor-submission-of-evidence-June-2012.doc

[16] AbbVie. *Glecaprevir/pibrentasvir for treating chronic hepatitis c [Appendices]: submission to National Institute for Health and Care Excellence. Single technology appraisal (STA)*. Maidenhead: AbbVie, 2017. 395p.

[17] AbbVie. *Glecaprevir with pibrentasvir (G/P) (Maviret) for treating HCV [ID1085] – Response to request for clarification from the ERG*. Maidenhead: AbbVie, 2017. 52p.

[18] Zeuzem S, Feld J, Wang S, Bourliere M, Wedemeyer H, Gane E, et al. ENDURANCE-1: a phase 3 evaluation of the efficacy and safety of 8- 12-week treatment with glecaprevir/pibrentasvir (formerly ABT-493/ABT-530) in HCV genotype 1-infected patients with or without HIV-1 co-infection and without cirrhosis. *The Liver Meeting; Nov 11-15, 2016*. Boston (MA): AASLD, 2016.

[19] Kowdley KV, Colombo M, Zadeikis N, Mantry PS, Calinas F, Aguilar H. ENDURANCE-2: safety and efficacy of glecaprevir/pibrentasvir in hepatitis C virus genotype 2-infected patients without cirrhosis: a randomized, double-blind, placebo-controlled study. *The Liver Meeting; Nov 11-15, 2016*. Boston (MA): AASLD, 2016.

[20] Foster GR, Gane E, Asatryan A, Pol S, Poordad F, Vierling J, et al. ENDURANCE-3: a phase 3, randomized, open-label, active-controlled study to compare efficacy and safety of ABT-493/ABT-530 to sofosbuvir co-administered with daclatasvir in adults with HCV genotype 3 infection. *European Association for the Study of the Liver, International Liver Congress; Apr 13-17, 2016*. Barcelona, Spain, 2016.

[21] Asselah T, Hezode C, Zadeikis N, Elkhashab M, Colombo M, Marinho R, et al. ENDURANCE-4: efficacy and safety of glecaprevir/pibrentasvir (formerly ABT-493/ABT-530) treatment in patients with chronic HCV genotype 4, 5, or 6 infection. *The Liver Meeting; Nov 11-15, 2016*. Boston (MA): AASLD, 2016.

[22] Muir AJ, Strasser S, Wang S, Shafran S, Bonacini M, Kwo PY, et al. High SVR rates with ABT-493 + ABT-530 co-administered for 8 weeks in non-cirrhotic patients with HCV genotype 3 infection. *European Association for the Study of the Liver, International Liver Congress; Apr 13-17, 2016*. Bardelona, Spain, 2016.

[23] Poordad F, Felizarta F, Wang S, Asatryan A, Hassanein T, Aguilar H, et al. High SVR rates with the combination of ABT493 + ABT530 for 8 weeks in noncirrhotic patients with HCV genotype 1 or 2 infection. *European Association for the Study of the Liver, International Liver Congress; Apr 13-17, 2016*. Barcelona, Spain, 2016.

[24] Wyles D, Poordad F, Wang S, Alric L, Felizarta F, Kwo PY, et al. SURVEYOR-II, part 3: efficacy and safety of glecaprevir/pibrentasvir (ABT-493/ABT-530) in patients with hepatitis C virus genotype 3 infection with prior treatment experience and/or cirrhosis. *The Liver Meeting; Nov 11-15, 2016*. Boston (MA): AASLD, 2016.

[25] Foster GR, Gane E, Asatryan A, Asselah T, Ruane PJ, Pol S, et al. ENDURANCE-3: safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naïve HCV genotype 3-infected patients without cirrhosis. *European Association for the Study of the Liver, International Liver Congress; Apr 19-23, 2017*. Amsterdam, the Netherlands, 2017.

[26] Forns X, Lee S, Valdes J, Lens S, Ghalib R, Aguilar H, et al. EXPEDITION-I: efficacy and safety of glecaprevir/pibrentasvir in adults with chronic hepatitis C virus genotype 1, 2, 4, 5 or 6 infection and compensated cirrhosis. *European Association for the Study of the Liver, International Liver Congress; Apr 19-23, 2017* Amsterdam, the Netherlands, 2017.

[27] Muir AJ, Strasser S, Wang S, Shafran S, Bonacini M, Kwo P, et al. High SVR rates with ABT-493 + ABT-530 co-administered for 8 weeks in non-cirrhotic patients with HCV genotype 3 infection. *European Association for the Study of the Liver, International Liver Congress; Apr 13-17, 2016*. Barcelona, Spain, 2016.

[28] Poordad F, Kwo PY, Hassanein T, Asatryan A, Wang S, Wyles D, et al. High SVR rates with ABT493 + ABT530 in noncirrhotic patients with HCV genotypes 1, 2, 3 infection. *Asian Pacific Association for the Study of the Liver; Feb 20-24, 2016*. Tokyo, Japan, 2016.

[29] Gane E, Poordad F, Wang S, Asatryan A, Kwo PY, Lalezari J, et al. High efficacy of ABT-493 and ABT-530 treatment in patients with HCV genotype 1 or 3 infection and compensated cirrhosis. *Gastroenterology* 2016;151(4):651-9 e1.

[30] Gane E, Poordad F, Asatryan A, Lalezari J, Hassanein T, Aguilar H, et al. High efficacy and favourable safety of ABT-493 + ABT-530 co-administration for 12 weeks in HCV genotype 1-infected patients with cirrhosis (SURVEYOR-I). *European Association for the Study of the Liver, International Liver Congress; Apr 13-17, 2016*. Barcelona, Spain, 2016.

[31] Poordad F, Felizarta F, Asatryan A, Sulkowski MS, Reindollar RW, Landis CS, et al. Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. *Hepatology* 2017;66(2):389-397.

[32] Rockstroh J, Lacombe K, Viani RM, Orkin C, Wyles D, Luetkemeyer A, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients co-infected with hepatitis C virus and human immunodeficiency virus-1: the EXPEDITION-2 Study. *European Association for the Study of the Liver, International Liver Congress; Apr 19-23, 2017* Amsterdam, the Netherlands, 2017.

[33] Reau N, Kwo PY, Rhee S, Brown RS, Agarwal K, Angus P, et al. MAGELLAN-2: safety and efficacy of glecaprevir/pibrentasvir in liver or renal transplant adults with chronic hepatitis C genotype 1-6 infection. *European Association for the Study of the Liver, International Liver Congress; Apr 19-23, 2017*. Amsterdam, the Netherlands, 2017.

[34] Gane E, Lawitz E, Pugatch D, Papatheodoridis G, Brau N, Brown A, et al. EXPEDITION-4: efficacy and safety of glecaprevir/pibrentasvir (ABT-430/ABT-530) in patients with renal impairment and chronic hepatitis C virus genotype 1-6 infection. *The Liver Meeting; Nov 11-15, 2016*. Boston (MA): AASLD, 2016.

[35] Poordad F, Gordon SC, Asatryan A, Felizarta F, Reindollar RW, Landis C, et al. High efficacy of ABT-493 and ABT-530 in HCV genotype 1-infected patients who have failed direct-acting antiviral-containing regimens: the MAGELLAN-I study. *European Association for the Study of the Liver, International Liver Congress; Apr 13-17, 2016*. Barcelona, Spain, 2016.

[36] Pilot-Matias T, Krishnan P, Schnell G, Tripathi R, Beyer J, Reisch T, et al. Resistance analysis in the MAGELLAN-1 study (part 2): glecaprevir/pibrentasvir therapy in HCV-infected patients who had failed prior DAA regimens containing NS3/4A protease and/or NS5A inhibitors. *European Association for the Study of the Liver, International Liver Congress; Apr 19-23, 2016*. Amsterdam, the Netherlands, 2017.

[37] Poordad F, Pol S, Asatryan A, Buti M, Shaw D, Hezode C, et al. MAGELLAN-1, part 2: glecaprevir and pibrentasvir for 12 or 16 weeks in patients with chronic hepatitis C virus genotype 1 or 4 and prior direct-acting antiviral treatment failure. *European Association for the Study of the Liver, International Liver Congress; Apr 19-23, 2016*. Amsterdam, the Netherlands, 2017.

[38] AbbVie. A study to evaluate the efficacy and safety of ABT-493/ABT-530 in subjects with genotype1 infection In: *ClinicalTrials.gov*, 2017 Jan 31 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02604017 NLM Identifier: NCT02604017

[39] AbbVie. *A randomized, open-label, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with dhronic hepatitis C virus genotype 1 infection (ENDURANCE-1): ABT-493/ABT-530 M13-590 clinical study report - post-treatment week 12 primary data R&D/16/0144*, 2016. 19248 p.

[40] AbbVie. A study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus (HCV) genotype 2 infection (ENDURANCE-2). In: *ClinicalTrials.gov*, 2017 Feb 21 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02640482 NLM Identifier: NCT02640482

[41] AbbVie. *A randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus genotype 2 infection (ENDURANCE-2): ABT-493/ABT-530 M15-464 clinical study report - post-treatment week 12 primary data R&D/16/0145*, 2016. 11929p.

[42] AbbVie. A study comparing efficacy and safety of ABT-493/ABT-530 to sofosbuvir dosed with daclatasvir in adults with HCV genotype 3 infection (ENDURANCE-3). In: *ClinicalTrials.gov*, 2017 Feb 8 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02640157 NLM Identifier: NCT02640157

[43] AbbVie. *A randomized, open-label, active-controlled, multicenter study to compare efficacy and safety of ABT-493/ABT-530 to sofosbuvir co-administered with daclatasvir in adults with chronic hepatitis C virus genotype 3 infection (ENDURANCE-3): ABT-493/ABT530 M13-594 clinical study report - post-treatment week 12 primary data R&D/16/0162*, 2016. 17703p.

[44] AbbVie. The efficacy and safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus genotype 4, 5, or 6 infection (ENDURANCE-4) In: *In ClinicalTrials.gov*, 2017 Jan 31 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02636595 NLM Identifier: NCT02636895

[45] AbbVie. *Single-arm, open-label study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus genotype 4, 5, or 6 infection (ENDURANCE-4): ABT-493/ABT-530 M13-583 clinical study report – post-treatment week 12 primary data R&D/16/0157*, 2016. 5127p.

[46] AbbVie. A study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus genotype 1, 2, 4, 5 or 6 infection and compensated cirrhosis (EXPEDITION-1). In: *In ClinicalTrials.gov*, 2017 Feb 10 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02642432 NLM Identifier: NCT02642432

[47] AbbVie. *A single arm, open-label study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus genotype 1, 2, 4, 5 or 6 infection and compensated cirrhosis (EXPEDITION-1): ABT-493/ABT-530 M14-172 clinical study report – post-treatment week 12 primary data R&D/16/0158*, 2016 [accessed 23.8.17]. 6963p.

[48] AbbVie. AbbVie presents new phase 2 data for investigational, once-daily, ribavirin-free, pan-genotypic regimen of ABT493 and ABT530 for hepatitis C genotypes 1-6. *European Association for the Study of the Liver, International Liver Congress; Apr 13-17, 2016*. Barcelona, Spain, 2016.

[49] Poordad F, Kwo PY, Hassanein T, Asatryan A, Wang S, Wyles D, et al. High SVR rates with ABT-493 + ABT-530 in non-cirrhotic patients with HCV genotypes 1, 2, 3 infection. *25th Conference of the Asian Pacific Association of the Study of the Liver; Feb 20-24, 2016*. Tokyo, Japan, 2016.

[50] Kwo P, Bennett M, Wang S, Vargas HE, Wyles D, Overcash JS, et al. SURVEYOR-II: high SVR rates achieved with next generation NS3/4A protease inhibitor ABT-493 and NHS5A inhibitor ABT-530 in non-cirrhotic treatment-naïve and treatment-experienced patients with HCV genotype 3 infection. *66th Annual Meeting of the American Association for the Study of Liver Diseases; Nov 13-17, 2015*. San Francisco (CA), 2015.

[51] AbbVie. A study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 with and without RBV in subjects with chronic hepatitis C virus (HCV) genotypes 2, 3, 4, 5 or 6 infection. In: *In ClinicalTrials.gov*, 2017 Feb 8 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02243293 NLM identifier: NCT02243293

[52] AbbVie. *A randomized, open-label, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 with and without ribavirin in subjects with chronic hepatitis c virus (HCV) genotypes 2, 3, 4, 5, or 6 infection (SURVEYOR-II): ABT-493, ABT-530, ABT-493/ABT-530 M14-868 clinical study report – primary analysis R&D/15/1230*, 2016. 40403p.

[53] AbbVie. *An open-label, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 with and without ribavirin in subjects with chronic hepatitis C virus (HCV) genotype 1, 4, 5, and 6 infection (SURVEYOR-I): ABT-493, ABT-530 M14-867 clinical study report R&D/15/1229*, 2016. 11311p.

[54] AbbVie. A study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 with and without ribavirin in subjects with HCV genotype 1, 4, 5, and 6 infection. In: *In ClinicalTrials.gov*, 2017 Feb 18 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02243280 NLM identifier: NCT02243280

[55] Gane E, Lalezari J, Asatryan A, Greenbloom S, Hassanein T, Ng TI, et al. 100% SVR4 and favorrable safety of ABT-493 + ABT-530 administered for 12 weeks in non-cirrhotic patients with genotypes 4, 5, or 6 infection (SURVEYOR-I). *European Association for the Study of the Liver, International Liver Congress; Apr 13-17, 2016*. Barcelona, Spain, 2016.

[56] Wyles D, Sulkowski M, Wang S, Bennett M, Vargas HE, Overcash JS, et al. SURVEYOR-II: high SVR4 rates achieved with the next generation NHS3/4A protease inhibitor ABT-493 and NS5A inhibitor ABT-530 in non-cirrhotic treatment-naitve and treatment-experienced patients with HCV genotype 2 infection. *66th Annual Meeting of the American Association for the Study of Liver Diseases; Nov 13-17, 2015*. San Francisco (CA), 2015.

[57] Hassanein T, Wyles D, Wang S, Kwo PY, Shiff ML, Younes Z, et al. SURVEYOR-II, part 4: glecaprevir/pibrentasvir demonstrates high SVR rates in patients with HCV genotype 2, 4, 5, or 6 infection without cirrhosis following an 8-week treatment duration. *The Liver Meeting; Nov 11-15, 2016*: AASLD, 2016.

[58] AbbVie. *Clinical study protocol M14-730: a multicenter, open-label study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus (HCV) genotype 1 – 6 infection and human immunodeficiency virus-1 (HIV-1) co-infection (EXPEDITION-2)*, 2016. 130p.

[59] AbbVie. *A single-arm, open-label, study to evaluate the efficacy and safety of ABT-493/ABT-530 in renally-impaired adults with chronic hepatitis C virus genotype 1 – 6 infection (EXPEDITION-4): ABT-493/ABT-530 M15-462 clinical study report – post-treatment week 12 primary data R&D/16/0159*, 2016. 7827p.

[60] AbbVie. A study to evaluate the efficacy and safety of ABT-493/ABT-530 in renally impaired adults with chronic hepatitis C virus genotype 1 - 6 infection (EXPEDITION-4). In: *In ClinicalTrials.gov*, 2017 Jan 31 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02651194 NLM identifier: NCT02651194

[61] AbbVie. *A randomized, open-label, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 (or ABT-493/ABT-530) with and without ribavirin in adults with chronic hepatitis C virus (HCV) infection who failed a prior direct-acting antiviral agent (DAA)-containing therapy: clinical study report R&D/16/0160 ABT-493, ABT-530, ABT-493/ABT-530 protocol M15-410 (primary analysis)*, 2016

[62] AbbVie. A study to evaluate the safety and efficacy of ABT-493/ABT-530 in adult post-liver or post-renal transplant recipients with chronic hepatitis C virus (MAGELLAN-2). In: *In ClinicalTrials.gov*, 2017 Jul 10 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02692703 NLM identifier: NCT02692703

[63] AbbVie. *Clinical study protocol M13-596: a single-arm, open-label, multicenter study to evaluate the safety and efficacy of ABT-493/ABT-530 in adult post-liver or post-renal transplant recipients with chronic hepatitis C virus genotype 1 – 6 infection (MAGELLAN-2)*, 2016. 116p.

[64] AbbVie. *A randomized, open-label, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in Japanese adults with chronic hepatitis C virus infection (CERTAIN-1): clinical study report R&D/16/0779 ABT-493/ABT-530/Protocol M15-594*, 2016. 12249p.

[65] Chayama K, Suzuki F, Karino Y, Kawakami Y, Sato K, Atarashi T, et al. CERTAIN-1: efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 1 hepatitis C virus infection with and without cirrhosis. *European Association for the Study of the Liver, International Liver Congress; Apr 19-23, 2017*. Amsterdam, the Netherlands, 2017.

[66] AbbVie. A study to evaluate the efficacy and safety of ABT-493/ABT-530 in Japanese adults with chronic hepatitis C virus infection (CERTAIN-1). In: *In ClinicalTrials.gov*, 2017 Feb 21 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02707952 NLM identifier: NCT02707952

[67] Chayama K, Suzuki F, Sato K, Atarashi T, Watanabe T, Toyoda H, et al. Efficacy and safety of glecaprevir/pirbrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection with and without cirrhosis. *European Association for the Study of the Liver, International Liver Congress; Apr 19-23, 2017*. Amsterdam, the Netherlands, 2017.

[68] AbbVie. A study to evaluate the efficacy and safety of ABT-493/ABT-530 in Japanese adults with genotype 2 chronic hepatitis C virus infection (CERTAIN-2). In: *In ClinicalTrials.gov*, 2017 May 11 [accessed 23.8.17]. Available from: https://clinicaltrials.gov/ct2/show/NCT02723084 NLM identifier: NCT02723084

[69] AbbVie. *A randomized, open-label, active comparator, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in Japanese adults with genotype 2 chronic hepatitis C virus infection (CERTAIN-2): clinical study report R&D/16/1258 ABT-493/ABT-530/Protocol M15-828*, 2016. 5175p.

[70] Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52(6):377-84.

[71] Welzel TZS, Dumas EO, Asselah T, Shaw D, Hazzan R, Forns X, et al. GARNET: 98% SVR rates following eight-week treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir for patients with HCV genotype 1b infection without cirrhosis. *Hepatol Int* 2017;11:S1002.

[72] Arama V, Catana R, L. S, Nastase RM, Molagic V, Radulescu M, et al. The efficacy of OBV/PTV/r + DSV and RBV in a Romanian cohort with genotype 1 HCV compensated cirrhosis. *Hepatol Int* 2017;11:S1028-S1029.

[73] Asselah T, Hezode C, Qaqish RB, ElKhashab M, Hassanein T, Papatheodoridis G, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin in adults with hepatitis C virus genotype 4 infection and cirrhosis (AGATE-I): a multicentre, phase 3, randomised open-label trial. *Lancet Gastroenterol Hepatol* 2016;1(1):25-35.

[74] Hezode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naïve and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. *Lancet* 2015;385(9986):2502-9.

[75] Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology* 2014;147(2):359-65.e1.

[76] Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014;370(21):1983-92.

[77] Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;370(21):1973-82.

[78] Feld JJ, Moreno C, Trinh R, Tam E, Bourgeois S, Horsmans Y, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12weeks. *J Hepatol* 2016;64(2):301-7.

[79] Lawitz E, Sullivan G, Rodriguez-Torres M, Bennett M, Poordad F, Kapoor M, et al. Exploratory trial of ombitasvir and ABT-450/r with or without ribavirin for HCV genotype 1, 2, and 3 infection. *J Infect* 2015;70(2):197-205.

[80] Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370(17):1594-603.

[81] Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlière M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370(17):1604-14.

[82] Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med* 2014;370(3):222-32.

[83] Dore GJ, Conway B, Luo Y, Janczewska E, Knysz B, Liu Y, et al. Efficacy and safety of ombitasvir/paritaprevir/r and dasabuvir compared to IFN-containing regimens in genotype 1 HCV patients: the MALACHITE-I/II trials. *J Hepatol* 2016;64(1):19-28.

[84] Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2015;385(9973):1075-86.

[85] Kwo P, Gane EJ, Peng CY, Pearlman B, Vierling JM, Serfaty L, et al. Effectiveness of elbasvir and grazoprevir combination, with or without ribavirin, for treatment-experienced patients with chronic hepatitis C infection. *Gastroenterology* 2017;152(1):164-75 e4.

[86] Sperl J, Horvath G, Halota W, Halota W, Ruiz-Tapiador JA, Streinu-Cercel A, et al. Efficacy and safety of elbasvir/grazoprevir and sofosbuvir/pegylated interferon/ribavirin: a phase III randomized controlled trial. *J Hepatol* 2016;65(6):1112-9.

[87] Foster G, Agarwal K, Cramp M, Moreea S, Barclay A, Collier J, et al. Elbasvir/grazoprevir plus sofosbuvir in treatment-naïve and treatment-experienced cirrhotic patients with hepatitis C virus genotype 3 infection treated for 8, 12, or 16 weeks: final results of the C-ISLE study. Paper presented at International Liver Congress 2017 - 52nd Annual meeting of the European Association for the Study of the Liver (EASL); 19-23 Apr 2017; Amsterdam: The Netherlands. *J Hepatol* 2017;66(Suppl 1):S503-4.

[88] Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ben Ari Z, Zhao Y, et al. Grazoprevir-elbasvir combination therapy for treatment-naïve cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. *Ann Intern Med* 2015;163(1):1-13.

[89] Gane EJ, Hyland RH, An D, Svarovskaia E, Pang PS, Brainard D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. *Gastroenterology* 2015;149(6):1454-61.e1.

[90] Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-

nucleoside inhibitor GS-9669 against HCV genotype 1 infection. *Gastroenterology* 2014;146(6):736-43.e1.

[91] Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014;370(20):1889-98.

[92] Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014;370(16):1483-93.

[93] Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014;370(20):1879-88.

[94] Abergel A, Asselah T, Metivier S, Kersey K, Jiang D, Mo H, et al. Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. *Lancet Infect Dis* 2016;16(4):459-64.

[95] Bourliere M, Bronowicki JP, de Ledinghen V, Hézode C, Zoulim F, Mathurin P, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis* 2015;15(4):397-404.

[96] Kohli A, Kapoor R, Sims Z, Nelson A, Sidharthan S, Lam B, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. *Lancet Infect Dis* 2015;15(9):1049-54.

[97] 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;373(27):2599-607.

[98] Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med* 2015;373(27):2608-17.

[99] 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;373(27):2618-28.

[100] Pianko S, Flamm SL, Shiffman ML, Kumar S, Strasser SI, Dore GJ, et al. Sofosbuvir plus velpatasvir combination therapy for treatment-experienced patients with genotype 1 or 3 hepatitis C virus infection: a randomized trial. *Ann Intern Med* 2015;163(11):809-17.

[101] Everson GT, Towner WJ, Davis MN, Wyles DL, Nahass RG, Thuluvath PJ, et al. Sofosbuvir with velpatasvir in treatment-naïve noncirrhotic patients with genotype 1 to 6 hepatitis C virus infection: a randomized trial. *Ann Intern Med* 2015;163(11):818-26.

[102] Wehmeyer MH, Jordan S, Luth S, Hartl J, Stoehr A, Eißing C, et al. Efficacy and safety of sofosbuvir-based triple therapy in hepatitis C genotype 4 infection. *Dig Liver Dis* 2015;47(9):811-4.

[103] Foster GR, Pianko S, Brown A, Forton D, Nahass RG, George J, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. *Gastroenterology* 2015;149(6):1462-70.

[104] Lawitz E, Poordad F, Brainard DM, Hyland RH, An D, Dvory-Sobol H, et al. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. *Hepatology* 2015;61(3):769-75.

[105] Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet* 2014;383(9916):515-23.

[106] Rodriguez-Torres M, Lawitz E, Kowdley KV, Kowdley KV, Nelson DR, Dejesus E, et al. Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naïve patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial. *J Hepatol* 2013;58(4):663-8.

[107] Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014;370(21):1993-2001.

[108] Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013;368(20):1867-77.

[109] Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013;368(20):1878-87.

[110] Lawitz E, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naïve patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis* 2013;13(5):401-8.

[111] Leroy V, Angus P, Bronowicki JP, Dore GJ, Hezode C, Pianko S, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: a randomized phase III study (ALLY-3+). *Hepatology* 2016;63(5):1430-41.

[112] Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015;61(4):1127-35.

[113] Hezode C, Leroy V, Rosa I, Roudot-Thoraval F, Pawlotsky J-M, de Ledinghen V, et al. Efficacy and safety of sofosbuvir and daclatasvir for 8 weeks in treatment-naïve non-cirrhotic patients with chronic hepatitis C virus genotype 3 infection. Paper presented at International Liver Congress 2017 - 52nd Annual meeting of the European Association for the Study of the Liver (EASL); 19-23 Apr 2017; Amsterdam: The Netherlands. *J Hepatol* 2017;66(Suppl 1):S299-300.

[114] Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014;370(3):211-21.

[115] Buti M, Calleja JL, Lens S, Diago M, Ortega E, Crespo J, et al. Simeprevir in combination with sofosbuvir in treatment-naïve and -experienced patients with hepatitis C virus genotype 4 infection: a phase III, open-label, single-arm study (PLUTO). *Aliment Pharmacol Ther* 2017;45(3):468-75.

[116] Pearlman BL, Ehleben C, Perrys M. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related child's class A cirrhosis. *Gastroenterology* 2015;148(4):762-70.e2; quiz e11-2.

[117] Lawitz E, Matusow G, DeJesus E, Yoshida EM, Felizarta F, Ghalib R, et al. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: a phase 3 study (OPTIMIST-2). *Hepatology* 2016;64(2):360-9.

[118] Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. *Lancet* 2014;384(9956):1756-65.

[119] Pol S, Ghalib RH, Rustgi VK, Martorell C, Everson GT, Tatum HA, et al. Daclatasvir for previously untreated chronic hepatitis C genotype-1 infection: a randomised, parallel-group, double-blind, placebo-controlled, dose-finding, phase 2a trial. *Lancet Infect Dis* 2012;12(9):671-7.

[120] Rodriguez-Torres M, Lawitz E, Yangco B, Jeffers L, Han SH, Thuluvath PJ, et al. Daclatasvir and peginterferon/ribavirin for black/African-American and Latino patients with HCV infection. *Ann Hepatol* 2016;15(6):834-45.

[121] Hezode C, Hirschfield GM, Ghesquiere W, Sievert W, Rodriguez-Torres M, Shafran SD, et al. Daclatasvir plus peginterferon alfa and ribavirin for treatment-naïve chronic hepatitis C genotype 1 or 4 infection: a randomised study. *Gut* 2015;64(6):948-56.

[122] Hezode C, Alric L, Brown A, Hassanein T, Rizzetto M, Buti M, et al. Randomized controlled trial of the NS5A inhibitor daclatasvir plus pegylated interferon and ribavirin for HCV genotype-4 (COMMAND-4). *Antivir Ther* 2015;21(3):195-205.

[123] Dore GJ, Lawitz E, Hézode C, Shafran SD, Ramji A, Tatum HA, et al. Daclatasvir plus peginterferon and ribavirin is noninferior to peginterferon and ribavirin alone, and reduces the duration of treatment for HCV genotype 2 or 3 infection. *Gastroenterology* 2015;148(2):355-366.e1.

[124] Zeuzem S, Hezode C, Bronowicki JP, Loustaud-Ratti V, Gea F, Buti M, et al. Daclatasvir plus simeprevir with or without ribavirin for the treatment of chronic hepatitis C virus genotype 1 infection. *J Hepatol* 2016;64(2):292-300.

[125] Hézode C, Almasio PL, Bourgeois S, Buggisch P, Brown A, Diago M, et al. Simeprevir and daclatasvir for 12 or 24 weeks in treatment-naïve patients with hepatitis C virus genotype 1b and advanced liver disease. *Liver Int* 2017;37(9):1304-13.

[126] Lagging M, Brown A, Mantry PS, Ramji A, Weilert F, Vierling JM, et al. Grazoprevir plus peginterferon and ribavirin in treatment-naïve patients with hepatitis C virus genotype 1 infection: a randomized trial. *J Viral Hepat* 2016;23(2):80-8.

[127] Manns MP, Vierling JM, Bacon BR, Bruno S, Shibolet O, Baruch Y, et al. The combination of MK-5172, peginterferon, and ribavirin is effective in treatment-naïve patients with hepatitis C virus genotype 1 infection without cirrhosis. *Gastroenterology* 2014;147(2):366-76.e6.

[128] Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. *N Engl J Med* 2013;368(1):45-53.

[129] Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014;384(9941):403-13.

[130] Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014;384(9941):414-26.

[131] Moreno C, Hezode C, Marcellin P, Bourgeois S, Francque S, Samuel D, et al. Efficacy and safety of simeprevir with PegIFN/ribavirin in naïve or experienced patients infected with chronic HCV genotype 4. *J Hepatol* 2015;62(5):1047-55.

[132] Fried MW, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobson I, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: the randomized PILLAR study. *Hepatology* 2013;58(6):1918-29.

[133] Manns M, Reesink H, Berg T, Dusheiko G, Flisiak R, Marcellin P, et al. Rapid viral response of once-daily TMC435 plus pegylated interferon/ribavirin in hepatitis C genotype-1 patients: a randomized trial. *Antivir Ther* 2011;16(7):1021-33.

[134] Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology* 2014;146(2):430-41.e6.

[135] Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. *Gastroenterology* 2014;146(7):1669-79.e3.

[136] Jensen D, Sherman KE, Hézode C, Pol S, Zeuzem S, de Ledinghen V, et al. Daclatasvir and asunaprevir plus peginterferon alfa and ribavirin in HCV genotype 1 or 4 non-responders. *J Hepatol* 2015;63(1):30-7.

[137] Everson GT, Sims KD, Rodriguez-Torres M, Hézode C, Lawitz E, Bourlière M, et al. Efficacy of an interferon- and ribavirin-free regimen of daclatasvir, asunaprevir, and BMS-791325 in treatment-naïve patients with HCV genotype 1 infection. *Gastroenterology* 2014;146(2):420-9.

[138] Food and Drug Administration. *Zepatier full prescribing information [Internet]*. Silver Spring (MD): FDA, 2016 [accessed 24.8.17]. 36p. Available from: https://www.merck.com/product/usa/pi_circulars/z/zepatier/zepatier_pi.pdf

[139] National Institute for Health and Care Excellence. *Sofosbuvir-velpatasvir for treating chronic hepatitis C. NICE technology appraisal guidance [TA430] [Internet]*. Manchester: NICE, 2017 [accessed 24.8.17]. 31p. Available from: nice.org.uk/guidance/ta430

[140] Riemsma R, Manuela J, Ramaekers B, Leadley R, Pouwels X, van Giessen A, et al. *Sofosbuvir in combination with velpatasvir for treating chronic hepatitis C*. York: Kleijnen Systematic Reviews, 2016. 109p.

[141] Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. *NICE DSU Technical Support Document 18: methods for population-adjusted indirect comparisons in submissions to NICE*. Sheffield: NICE Decision Support Unit, 2016. 81p.

[142] Nixon R, Bergvall N, Tomic D, Sfikas N, Cutter G, Giovannoni G. No evidence of disease activity: indirect comparisons of oral therapies for the treatment of relapsing-remitting multiple sclerosis. *Adv Ther* 2014;31(11):1134-54.

[143] Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Stat Med* 2002;21:1575-600.

[144] Di Lorenzo G, Casciano R, Malangone E, Buonerba C, Sherman S, Willet J, et al. An adjusted indirect comparison of everolimus and sorafenib therapy in sunitinib-refractory metastatic renal cell carcinoma patients using repeated matched samples. *Expert Opin Pharmaco* 2011;12:1491-7.

[145] Johnson SJ, Parise H, Virabhak S, Filipovic I, Samp JC, Misurski D. Economic evaluation of ombitasvir/paritaprevir/ritonavir and dasabuvir for the treatment of chronic genotype 1 hepatitis C virus infection. *J Med Econ* 2016;19(10):983-94.

[146] McEwan P, Selvapatt N, Brown A, Thursz M, Bennett H, Webster S, et al. A clinician's guide to the cost and health benefits of hepatitis C cure assessed from the individual patient perspective. *Eur J Gastroenterol Hepatol* 2017;29(2):208-14.

[147] National Institute for Health and Care Excellence. *Single technology appraisal: elbasvir-grazoprevir for treating chronic hepatitis C [ID842]*. Manchester: NICE, 2016. 730p.

[148] Faria R, Woods B, Griffin S, Palmer S, Sculpher M, Ryder SD. Prevention of progression to cirrhosis in hepatitis C with fibrosis: effectiveness and cost effectiveness of sequential therapy with new direct-acting anti-virals. *Aliment Pharmacol Ther* 2016;44(8):866-76.

[149] Connoly M, Kotsopoulos N. Assessing the long-term fiscal consequences attributed to hepatitis C and the impact of ledipasvir / sofosbuvir combination curative therapies in UK. *Hepatology* 2016;64:53.

[150] Selvapatt N, Ward T, Ananthavarathan A, Khan B, Webster S, Thursz M, et al. Cost-effectiveness of birth cohort screening and treatment for HCV in the UK: an exploratory analysis. *J Hepatol* 2016;64(Suppl 2):S465.

[151] Thokala P, Simpson EL, Tappenden P, Stevens JW, Dickinson K, Ryder S, et al. Ledipasvir-sofosbuvir for treating chronic hepatitis C: a NICE single technology appraisal - an evidence review group perspective. *PharmacoEcon* 2016;34(8):741-50.

[152] Westerhout KY, Treur M, Mehnert A, Pascoe K, Ladha I, Belsey J. Cost-utility analysis of simeprevir with peginterferon + ribavirin (SMV/PR) in the management of genotype 1 (G1) and 4 (G4) hepatitis C virus (HCV) infection; from the perspective of the UK National Health Service (NHS). *Value Health* 2014;17(7):A679.

[153] 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;10(21):1-113, iii.

[154] Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2007;11(11):1-205, iii.

[155] Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(17):i-xii, 1-210.

[156] National Institute for Health and Care Excellence. *Ombitasvir-paritaprevir-ritonavir with or without dasabuvir for treating chronic hepatitis C. NICE technology appraisal guidance [TA362] [Internet]*. Manchester: NICE, 2015 [accessed 30.8.17]. 58p. Available from: http://nice.org.uk/guidance/ta365

[157] Eastern Liver Network. *Management of hepatitis C: hepatitis C guidelines v 8.1. 09 June 2017*. Cambridge: Eastern Liver Network, 2017. 7p.

[158] Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008;48(2):418-31.

[159] Kanwal F, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. veterans with HCV. *Hepatology* 2014;60(1):98-105.

[160] Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112(2):463-72.

[161] Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. *Liver Transpl* 2002;8(3):263-70.

[162] Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. *Ann Intern Med* 2012;156(4):279-90.

[163] Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis* 2011;52(7):889-900.

[164] Morisco F, Granata R, Stroffolini T, Guarino M, Donnarumma L, Gaeta L, et al. Sustained virological response: a milestone in the treatment of chronic hepatitis C. *World J Gastroenterol* 2013;19(18):2793-8.

[165] Papastergiou V, Stampori M, Lisgos P, Pselas C, Prodromidou K, Karatapanis S. Durability of a sustained virological response, late clinical sequelae, and long-term changes in aspartate aminotransferase to the platelet ratio index after successful treatment with peginterferon/ribavirin for chronic hepatitis C: a prospective study. *Eur J Gastroenterol Hepatol* 2013;25(7):798-805.

[166] Koh C, Heller T, Haynes-Williams V, Hara K, Zhao X, Feld JJ, et al. Long-term outcome of chronic hepatitis C after sustained virological response to interferon-based therapy. *Aliment Pharmacol Ther* 2013;37(9):887-94.

[167] Veldt BJ, Saracco G, Boyer N, C. C, Bellobuono A, Hopf U, et al. Long term clinical outcome of chronic hepatitis C patients with sustained virological response to interferon monotherapy. *Gut* 2004;53(10):1504-8.

[168] Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002;122(5):1303-13.

[169] Lee SH, Jin YJ, Shin JY, Lee JW. Assessment of hepatocellular carcinoma risk based on peg-interferon plus ribavirin treatment experience in this new era of highly effective oral antiviral drugs. *Medicine (Baltim)* 2017;96(1):e5321.

[170] Janjua NZ, Chong M, Kuo M, Woods R, Wong J, Yoshida EM, et al. Long-term effect of sustained virological response on hepatocellular carcinoma in patients with hepatitis C in Canada. *J Hepatol* 2017;66(3):504-13.

[171] Aleman S, Rahbin N, Weiland O, Davidsdottir L, Hedenstierna M, Rose N, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. *Clin Infect Dis* 2013;57(2):230-6.

[172] Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology* 2010;52(3):833-44.

[173] Office for National Statistics. National life tables, UK: 2013-2015 [Internet]. London: ONS, 2016 [accessed 8.8.17]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/20132015

[174] Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. *JAMA* 2003;290(2):228-37.

[175] Grieve R, Roberts J, Wright M, Sweeting M, DeAngelis D, Rosenberg W, et al. Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. *Gut* 2006;55(9):1332-8.

[176] National Institute for Health and Care Excellence. *Final appraisal determination. Sofosbuvir-velpatasvir for treating chronic hepatitis C [Internet]*. Manchester: NICE, 2016 [accessed 15.9.17] Available from: https://www.nice.org.uk/guidance/ta430/documents/final-appraisal-determination-document

[177] National Institute for Health and Care Excellence. *Daclatasvir for treating chronic hepatitis C. NICE technology appraisal guidance [TA364] [Internet]*. Manchester: NICE, 2015 [accessed 15.9.17] Available from: https://www.nice.org.uk/guidance/ta364

[178] Grishchenko M, Grieve RD, Sweeting MJ, Angelis D, Thomson BJ, Ryder SD, et al. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. *Int J Technol Assess Health Care* 2009;25(2):171-80.

[179] Madin-Warburton M, Pitcher A, Martin N. The impact of dynamic transmission modelling on the estimated cost-effectiveness of treatment for chronic hepatitis C in the UK. MO3. Paper presented at ISPOR 19th Annual European Congress; 29 Oct-2 Nov 2016; Vienna: Austria. *Value Health* 2016;19(7):A347.

[180] Adelphi Research UK. *HCV market tracker - UK. Final data: November 2016. Project reference 22968 [PowerPoint presentation]*: AbbVie, 2017. 70 p.

[181] National Institute for Health and Care Excellence. *Hepatitis C (genotype 1) - boceprevir. Single technology appraisal [TA253]*. Manchester: NICE, 2011 338p.

[182] Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol* 2010;52(5):652-7.

[183] Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth BM, et al. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut* 2003;52(3):425-32.

[184] Liver Advisory Group. *Liver transplantation: selection criteria and recipient registration. Policy POL 195/6*. Watford: NHS Blood and Transplant, 2017. 30p.

[185] Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997;127(10):855-65.

[186] Cheung MCM, Foster GR, Irving WL, Walker AJ, Hudson BE, Verma S, et al. UK EAP antiviral treatment in patients with advanced HCV cirrhosis using sofosbuvir and ledipasvir/ daclatasvir, with or without ribavirin outcomes compared to untreated patients and long term outcomes..... antiviral treatment in patients with advanced HCV cirrhosis using sofosbuvir and ledipasvir/ daclatasvir with or without ribavirin 6 and 12 month outcomes compared to untreated patients. *European Association for the Study of the Liver, International Liver Congress; Apr 13-17, 2016.* Barcelona, Spain, 2016.

[187] Siebert U, Sroczynski G, Wasem J, Greiner W, Ravens-Sieberer U, Aidelsburger P, et al. Using competence network collaboration and decision-analytic modeling to assess the cost-effectiveness of interferon alpha-2b plus ribavirin as initial treatment of chronic hepatitis C in Germany. *Eur J Health Econ* 2005;6(2):112-23.

[188] Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. *Gastroenterology* 2017;153(1):113-22.

[189] Foster GR, Zeuzem S, Gane E, Stedman C, Feld JJ, Mangia A, et al. Sofosbuvir-based all-oral regimens for patients with chronic hepatitis C genotype 3 infection: integrated analysis of five clinical studies. Paper presented at The 67th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2016; 11-15 Nov 2016; Boston: United States. *Hepatology* 2016;64(Suppl 1):955A.

[190] AbbVie. *A randomized, open-label study to evaluate the safety and efficacy of coadministration of ABT-450 with ritonavir (ABT-450/r) and ABT-267 in adults with chronic hepatitis C virus infection (PEARL-I): clinical study report R&D/14/0577 ABT-450, ritonavir, and ABT-267/pProtocol M13-393*. North Chicago (IL), 2014. 315p.

[191] AbbVie. *Data on File: AGATE-I CSR*

[192] Abergel A, Metivier S, Samuel D, Jiang D, Kersey K, Pang PS, et al. Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. *Hepatology* 2016;64(4):1049-56.

[193] AbbVie. *Data on File: TURQUOISE-III CSR*

[194] Vera-Llonch M, Martin M, Aggarwal J, Donepudi M, Bayliss M, Goss T, et al. Health-related quality of life in genotype 1 treatment-naïve chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. *Aliment Pharmacol Ther* 2013;38(2):124-33.

[195] AbbVie. *Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use [package insert]*. North Chicago (IL): AbbVie, 2014

[196] Gilead Sciences Ltd. *Epclusa 400 mg/100 mg film coated tablets: summary of product characteristics [Internet]*. Leatherhead, 2017 [accessed 22.9.17] Available from: https://www.medicines.org.uk/emc/medicine/32177

[197] Puoti M, Foster GR, Wang S, Mutimer D, Gane E, Moreno C, et al. High SVR rates with eight and twelve weeks of pangenotypic glecaprevir/pibrentasvir: integrated efficacy analysis of genotypes 1-6 patients without cirrhosis. Paper presented at International Liver Congress 2017 - 52nd Annual meeting of the European Association for the Study of the Liver (EASL); 19-23 Apr 2017; Amsterdam: The Netherlands. *J Hepatol* 2017;66(Suppl 1):S721.

[198] Joint Formulary Committee. *British National Formulary, 69*. London: BMJ Group and Pharmaceutical Press, 2016.

[199] Personal Social Services Research Unit. *Unit Costs of Health and Social Care*. Canterbury: University of Kent, 2016 [accessed 15.9.17] Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php

[200] Thorlund K, Druyts E, El Khoury AC, Mills EJ. Budget impact analysis of boceprevir and telaprevir for the treatment of hepatitis C genotype 1 infection. *Clinicoecon Outcomes Res* 2012;4:349-59.

[201] National Institute for Health and Care Excellence. *Depression in adults: recognition and management. NICE clinical guidance [CG90] [Internet]*. Manchester: NICE, 2009 [accessed 15.9.17] Available from: https://www.nice.org.uk/guidance/cg90

[202] Backx M, Lewszuk A, White JR, Cole J, Sreedharan A, van Sanden S, et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. *J Viral Hepat* 2014;21(3):208-15.

[203] Singh J, Longworth L. Estimating the cost of liver transplantation in patients diagnosed with chronic hepatitis C and B in the UK. *Value Health* 2014;17(7):A368.

[204] AbbVie. *Cost-effectiveness of AbbVie's next generation pan-genotypic hepatitis C virus (HCV) antiviral treatment [ID1085]: glecaprevir-pibrentasvir economic model final. Company evidence submission*. Maidenhead: AbbVie, 2017

[205] Strong M, Oakley JE, Brennan A. Estimating multiparameter partial expected value of perfect information from a probabilistic sensitivity analysis sample: a nonparametric regression approach. *Med Decis Making* 2014;34(3):311-26.

[206] Brady B, Siebert U, Sroczynski G, Murphy G, Husereau D, Sherman M, et al. *Pegylated interferon combined with ribavirin for chronic hepatitis C virus infection: an economic evaluation [Technology Report no 82]*. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2007

[207] Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001;34(1 Pt 1):809-16.

[208] Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin Liver Dis* 2000;20(1):17-35.

[209] Seeff LB. The history of the "natural history" of hepatitis C (1968-2009). *Liver Int* 2009;29(Suppl 1):89-99.

[210] Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;13(5):509-18.

[211] Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: a systematic review and meta-analysis. *Clin Infect Dis* 2016;62(6):683-94.

Appendix 1: Further critique of searches in the company submission

- Using both American and UK spellings would have helped improve the thoroughness of searching. For example,"randomized controlled trial"[Title/Abstract] in the clinical effectiveness searches should have been "randomized controlled trial" or "randomised controlled trial" ; "cost AND minimization AND analysis" in Appendix A3 should have been: "cost AND minimization AND analysis" or "cost AND minimisation AND analysis"
- It is redundant to search for "random$"[Title/Abstract] and "randomization"[Title/Abstract] as the truncated random$ will find randomization. This is the same for "placebo$"[Title/Abstract] which will find both placebo and placebos.
- Searching for CAS numbers for drugs would have helped improve the thoroughness of the searching. For example 1365970-03-1 for glecaprevir.
- Additional synonyms could have also been added to searches for some of the drugs. For example hepcinat, hepcvir, sovihep and resof are all synonyms for sofosbuvir that could have been looked for.
- Time could have been saved by using a MeSH browser to find the correct MeSH headings. For example, there is no MeSH for "crossover procedure", "double-blind procedure" or "non a non be hepatitis" so no need to search for these using MeSH.
- Looking up the correct terms for EMTREE would also save time. For example, "hepatitis non A non B" is the correct EMTREE term and not "non a non b hepatitis" which was also searched for as an EMTREE term.
- There are also a number of EMTREE terms for the interventions of interest which were not looked for. For example, sofosbuvir, velpatasvir, elbasvir, ombitasvir, ledipasvir, daclatasvir, grazoprevir, simeprevir, paritaprevir, pibrentasvir and glecaprevir all have EMTREE headings.
- Parentheses were poorly applied in a number of Embase searches. For example:

#4	(((**quality** AND **adjusted** AND **life** AND year$ OR qaly$ OR **life**) AND year$ AND **gained** OR **life**) AND year$ AND equivalent$ OR **incremental**) AND **cost** AND effective$ OR **icer**	**13800**

A more faithful update of the original TA430 search would have been:

((quality adjusted life year$ OR qaly$) OR (life year$ gained) OR (life year$ equivalent$) OR (incremental cost effective$) OR (icer))

Appendix 2: List price base-case incremental cost effectiveness results

This appendix presents the base-case incremental cost effectiveness results summarised as reported by the company in Appendix B14 in the clarification responses.[17] The cost effectiveness results in the CS, were obtained from an early version of the economic model which was acknowledged by the company as an (cf. response to Question B14 in the clarification letter).[17] The results presented below are based on list prices for G/P and all comparators.

GT1 patients

Table A.1: List price base-case incremental cost effectiveness analysis results for GT1 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	19,514	18.77	12.66	NA
G/P	27,657	20.40	16.30	2,239
SOF/LDV	28,437	20.34	16.15	Dominated
3D/2D	37,718	20.38	16.23	Dominated
EBR/GZR	39,224	20.31	16.08	Dominated
SOF/VEL	40,860	20.39	16.28	Dominated

Source: Table 1 – Appendix B14 in response to the clarification letter.[17]
DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.2: List price base-case incremental cost effectiveness analysis results for GT1 TN CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	43,322	13.35	7.13	NA
EBR/GZR	53,678	17.40	10.34	3,228
G/P	55,208	17.57	10.49	10,633
SOF/VEL	55,513	17.51	10.44	Dominated
SOF/LDV	56,509	17.32	10.28	Dominated
3D/2D	76,663	17.42	10.35	Dominated

Source: Table 2 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.3: List price base-case incremental cost effectiveness analysis results for GT1 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	20,977	17.99	11.92	NA
G/P	27,604	19.82	15.49	1,855
3D/2D	37,695	19.79	15.42	Dominated
EBR/GZR	39,248	19.71	15.28	Dominated
SOF/VEL	40,849	19.81	15.47	Dominated
SOF/LDV	41,519	19.75	15.35	Dominated

Source: Table 3 – Appendix B14 in response to the clarification letter.[17]
DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

Table A.4: List price base-case incremental cost effectiveness analysis results for GT1 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	42,629	13.18	7.04	NA
EBR/GZR	54,017	16.89	10.02	3,824
SOF/VEL	55,132	17.11	10.20	6,144
G/P	56,016	16.99	10.11	Dominated
SOF/LDV	58,542	16.62	9.80	Dominated
3D/2D	75,680	17.11	10.19	Dominated

Source: Table 4 – Appendix B14 in response to the clarification letter.[17]

CC = compensated cirrhosis; DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

GT2 patients

Table A.5: List price base-case incremental cost effectiveness analysis results for GT2 TN NC patients (IFN-eligible)

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
Peg-IFN + RBV	9,847	20.25	15.76	NA
No treatment	15,238	19.49	13.52	Dominated
G/P	27,557	20.41	16.30	32,704

Source: Table 5 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; Peg-IFN = pegylated IFN; QALY = quality-adjusted life year; RBV = ribavirin; TN = treatment-naïve

Table A.6: List price base-case incremental cost effectiveness analysis results for GT2 TN NC patients (IFN-ineligible)

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	15,238	19.49	13.52	NA
G/P	27,557	20.41	16.30	4,433
SOF/RBV	37,839	20.39	16.22	Dominated
SOF/VEL	40,619	20.41	16.31	1,710,917

Source: Table 6 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve

Table A.7: List price base-case incremental cost effectiveness analysis results for GT2 TN CC patients (IFN-eligible)

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	44,514	13.98	7.48	NA
SOF/VEL	55,041	17.57	10.49	3,498
G/P	55,208	17.57	10.49	Dominated

Source: Table 7 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.8: List price base-case incremental cost effectiveness analysis results for GT2 TN CC patients (IFN-ineligible)

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	44,514	13.98	7.48	NA
SOF/RBV	54,848	17.20	10.17	Extended dominance
SOF/VEL	55,041	17.57	10.49	3,498
G/P	55,208	17.57	10.49	Dominated

Source: Table 8 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.9: List price base-case incremental cost effectiveness analysis results for GT2 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	17,098	18.69	12.72	NA
G/P	28,745	19.74	15.28	4,550
SOF/RBV	39,472	19.70	15.19	Dominated
SOF/VEL	40,444	19.83	15.52	47,391

Source: Table 9 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

Table A.10: List price base-case incremental cost effectiveness analysis results for GT2 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	43,738	13.78	7.37	NA
SOF/VEL	54,665	17.17	10.25	3,804
G/P	54,832	17.17	10.25	Dominated
SOF/RBV*	58,295	16.40	9.58	Dominated

Source: Table 10 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir
* Reporting in the table provided by the company. Corrected based on the electronic model.

GT3 patients

Table A.11: List price base-case incremental cost effectiveness analysis results for GT3 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	22,440	18.03	11.92	NA
G/P	28,619	20.30	16.11	1,475
SOF/VEL	40,826	20.38	16.26	83,021
SOF/DCV	61,608	20.35	16.19	Dominated

Source: Table 11 – Appendix B14 in response to the clarification letter.[17]
DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.12: List price base-case incremental cost effectiveness analysis results for GT3 TN CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	42,077	12.69	6.78	NA
G/P	55,604	17.49	10.43	3,703
SOF/VEL	55,874	17.41	10.36	Dominated
SOF/PR	56,027	17.15	10.12	Dominated
SOF/RBV	93,001	16.48	9.62	Dominated
SOF/DCV	129,294	17.57	10.45	3,106,990

Source: Table 12 – Appendix B14 in response to the clarification letter.[17]
Abbreviations: CC = compensated cirrhosis; DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; peg-IFN = pegylated IFN; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.13: List price base-case incremental cost effectiveness analysis results for GT3 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	23,577	17.28	11.23	NA
SOF/PR	40,436	19.69	15.24	4,214
SOF/VEL	42,376	19.61	15.15	Dominated
G/P	54,675	19.72	15.33	157,141
SOF/DCV	62,256	19.68	15.26	Dominated

Source: Table 13 – Appendix B14 in response to the clarification letter.[17]
DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; peg-IFN = pegylated IFN; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

Table A.14: List price base-case incremental cost effectiveness analysis results for GT3 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	41,467	12.54	6.70	NA
SOF/PR	57,088	16.51	9.70	Extended dominance
SOF/VEL	57,265	16.70	9.89	4,952
G/P	69,411	16.89	10.03	81,987
SOF/RBV	97,406	15.27	8.76	Dominated
SOF/DCV	128,918	17.17	10.21	336,033

Source: Table 14 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; peg-IFN = pegylated IFN; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

GT4 patients

Table A.15: List price base-case incremental cost effectiveness analysis results for GT4 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	18,786	18.90	12.81	NA
G/P	28,657	20.30	16.06	3,033
OBV/PTV/RTV	35,017	20.42	16.33	23,580
EBR/GZR	37,989	20.42	16.33	Dominated
SOF/VEL	40,573	20.42	16.34	1,203,376

Source: Table 15 – Appendix B14 in response to the clarification letter.[17]

EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.16: List price base-case incremental cost effectiveness analysis results for GT4 TN CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	43,442	13.41	7.17	NA
OBV/PTV/RTV	49,957	17.43	10.38	2,031
EBR/GZR	52,551	17.57	10.48	25,133
SOF/VEL	55,135	17.57	10.49	373,179
G/P	55,208	17.57	10.49	Dominated
SOF/LDV	55,273	17.57	10.48	Dominated

Source: Table 16 – Appendix B14 in response to the clarification letter.[17]

CC = compensated cirrhosis; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.17: List price base-case incremental cost effectiveness analysis results for GT4 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	20,320	18.11	12.05	NA
G/P	27,271	19.83	15.52	2,005
OBV/PTV/RTV	34,980	19.83	15.51	Dominated
EBR/GZR	37,935	19.83	15.52	Dominated
SOF/VEL	40,538	19.83	15.52	3,858,701
SOF/LDV	43,619	19.57	14.98	Dominated

Source: Table 17 – Appendix B14 in response to the clarification letter.[17]
EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

Table A.18: List price base-case incremental cost effectiveness analysis results for GT4 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	42,741	13.24	7.08	NA
OBV/PTV/RTV	49,141	17.10	10.19	2,055
SOF/VEL	54,759	17.17	10.25	101,059
G/P	54,832	17.17	10.25	Dominated
SOF/LDV	54,897	17.17	10.24	Dominated
EBR/GZR	61,267	15.86	9.18	Dominated

Source: Table 18 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

GT5 patients

Table A.19: List price base-case incremental cost effectiveness analysis results for GT5 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	18,786	18.90	12.81	NA
G/P	27,306	20.42	16.33	2,417
SOF/VEL	41,179	20.37	16.22	Dominated

Source: Table 19 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.20: List price base-case incremental cost effectiveness analysis results for GT5 TN CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	43,442	13.41	7.17	NA
SOF/VEL	55,135	17.57	10.49	3,524
G/P	55,208	17.57	10.49	Dominated
SOF/PR	67,669	15.49	8.79	Dominated

Source: Table 20 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis = G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; peg-IFN = pegylated IFN; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.21: List price base-case incremental cost effectiveness analysis results for GT5 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	20,320	18.11	12.05	NA
G/P	27,271	19.83	15.52	2,005
SOF/VEL	40,538	19.83	15.52	3,858,701

Source: Table 21 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

Table A.22: List price base-case incremental cost effectiveness analysis results for GT5 TE CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	42,741	13.24	7.08	NA
SOF/VEL	54,759	17.17	10.25	3,791
G/P	54,832	17.17	10.25	Dominated
SOF/PR	67,130	15.20	8.62	Dominated

Source: Table 22 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis = G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; peg-IFN = pegylated IFN; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

GT6 patients

Table A.23: List price base-case incremental cost effectiveness analysis results for GT6 TN NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	18,786	18.90	12.81	NA
G/P	29,501	20.23	15.89	3,473
SOF/VEL	40,573	20.42	16.34	24,958

Source: Table 23 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.24: List price base-case incremental cost effectiveness analysis results for GT6 TN CC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	43,442	13.41	7.17	NA
SOF/VEL	55,135	17.57	10.49	3,524
G/P	55,208	17.57	10.49	Dominated
SOF/PR	67,669	15.49	8.79	Dominated

Source: Table 24 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis = G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; peg-IFN = pegylated IFN; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

Table A.25: List price base-case incremental cost effectiveness analysis results for GT6 TE NC patients

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	20,320	18.11	12.05	NA
G/P	27,271	19.83	15.52	2,005
SOF/VEL	40,538	19.83	15.52	3,858,701

Source: Table 25 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

Table A.26: List price base-case incremental cost effectiveness analysis results for GT6 TE CC patients

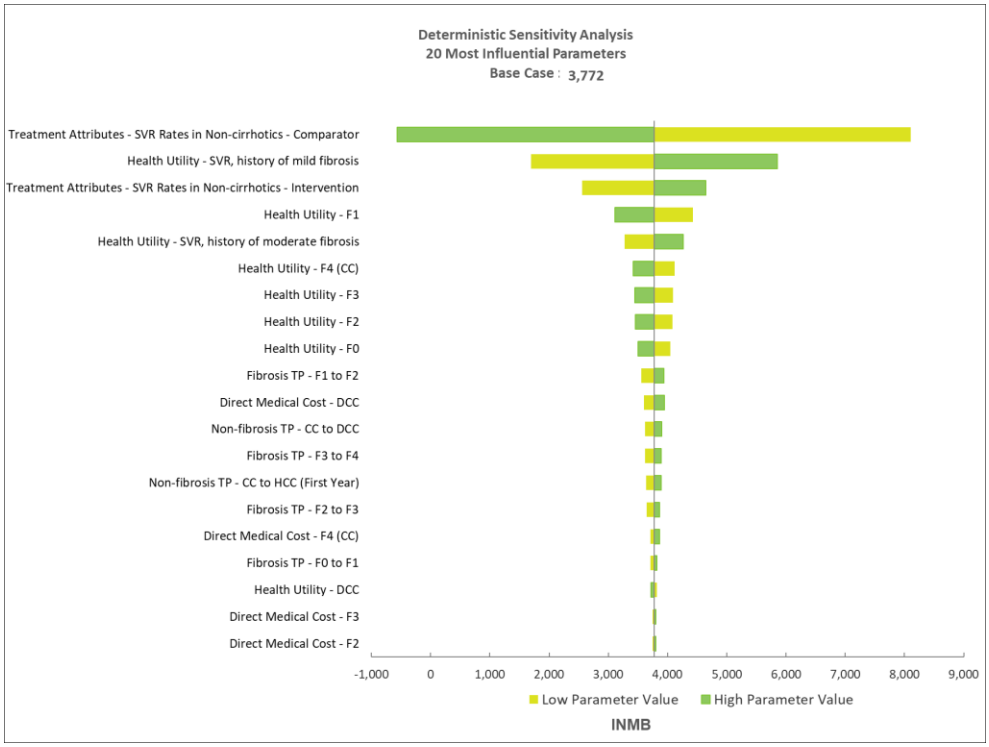
Technologies	Total costs (£)	Total LYG	Total QALYs	ICER incremental (£/QALY)
No treatment	42,741	13.24	7.08	NA
SOF/VEL	54,759	17.17	10.25	3,791
G/P	54,832	17.17	10.25	Dominated
SOF/PR	67,130	15.20	8.62	Dominated

Source: Table 26 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis = G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; peg-IFN = pegylated IFN; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

Deterministic sensitivity analysis

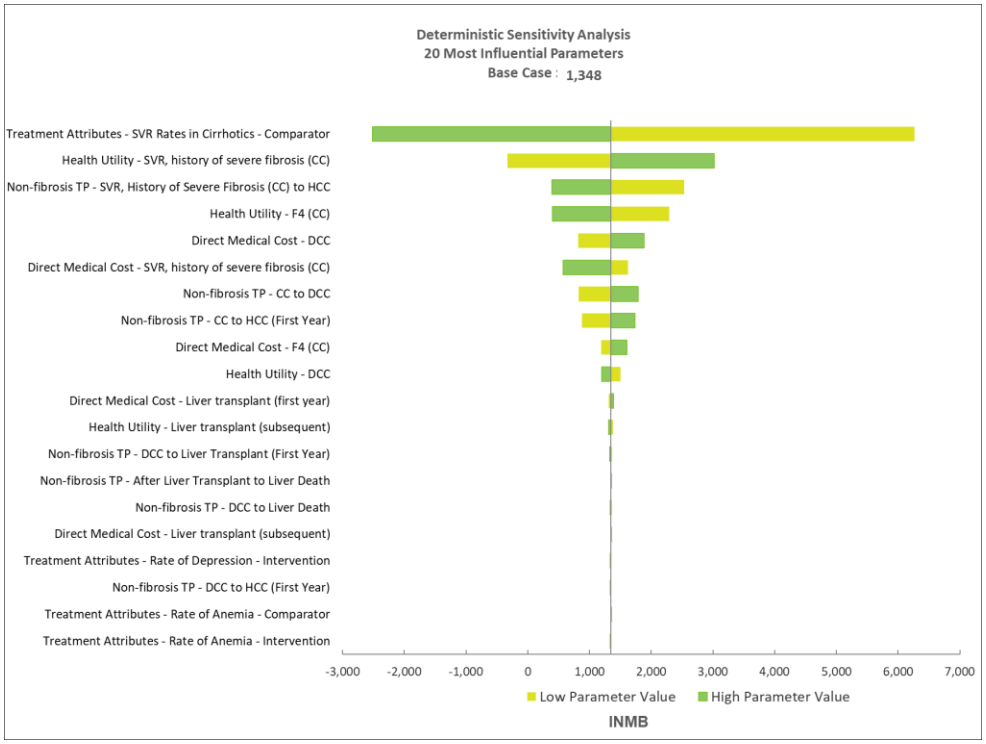
In this section, the tornado diagrams for the 26 patient subgroups described in Section 5.2.3 of this report are presented. These tornado diagrams were built by the company based on the INMB of G/P against one relevant comparator for each subgroup at a threshold of £20,000 per QALY. The diagrams were reported in response to the clarification letter in Appendix F.[17] The ERG noticed an inconsistency in one of the tornado diagrams reported by the company, which did not match the one produced by the electronic model. The ERG assumed that the diagram obtained from the model was the correct one and it is the one shown in this appendix. This was for the GT3 TN NC subgroup (Figure A.12 below).

Figure A.1: Tornado diagram: GT1 TN NC, G/P vs. SOF/LDV



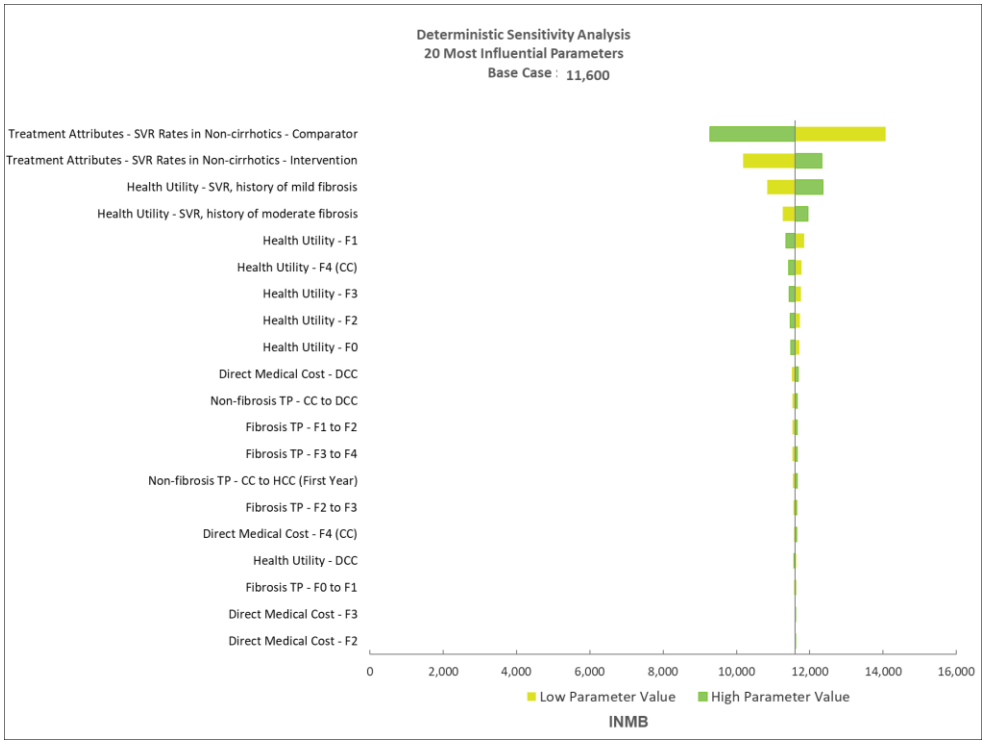
Source: response to clarification letter Appendix F.[17]

Figure A.2: Tornado diagram: GT1 TN CC, G/P vs. EBR/GZR



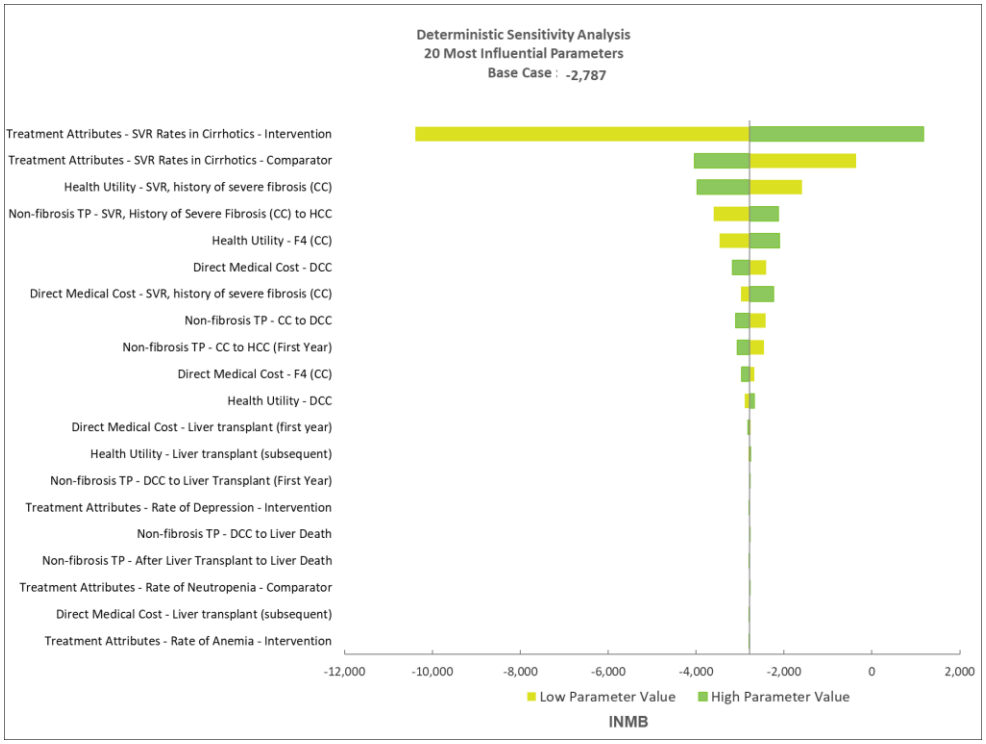
Source: response to clarification letter Appendix F.[17]

Figure A.3: Tornado diagram: GT1 TE NC, G/P vs. OBV/PTV/RTV + DSV



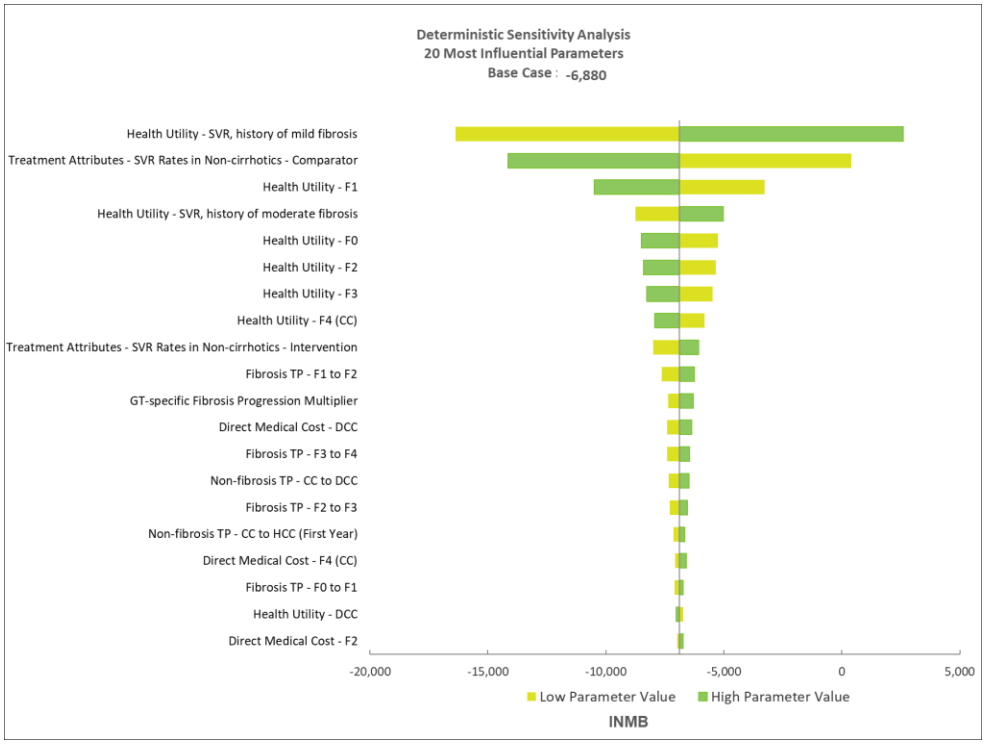
Source: response to clarification letter Appendix F.[17]

Figure A.4: Tornado diagram: GT1 TE CC, G/P vs. SOF/VEL



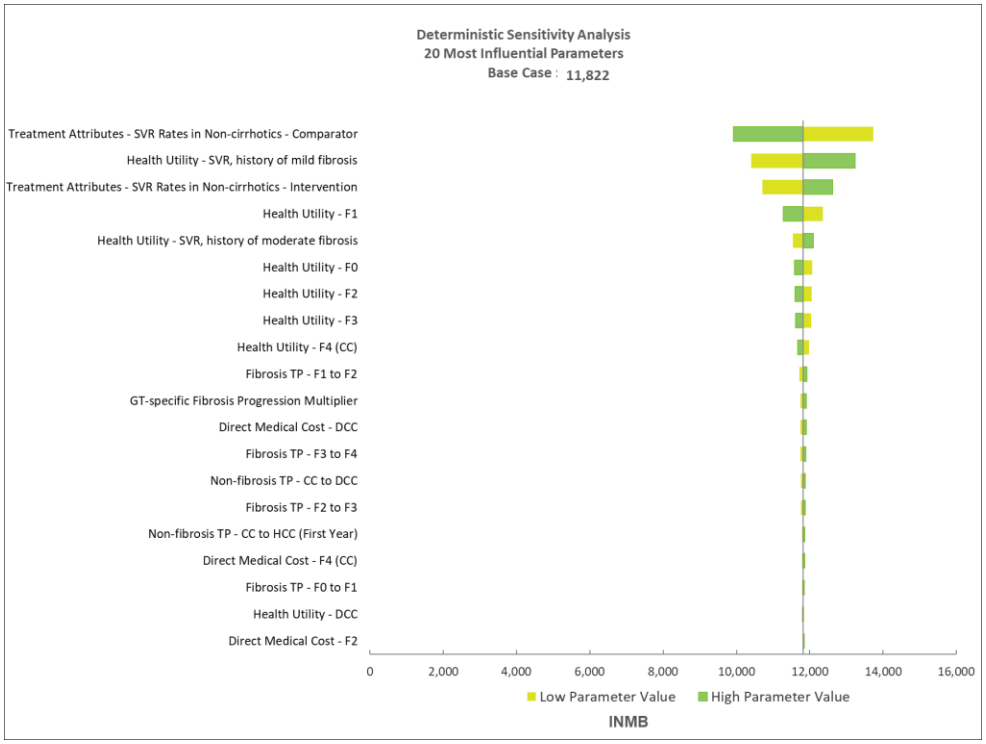
Source: response to clarification letter Appendix F.[17]

Figure A.5: Tornado diagram: GT2 TN NC IFN-eligible, G/P vs. peg-IFN + RBV



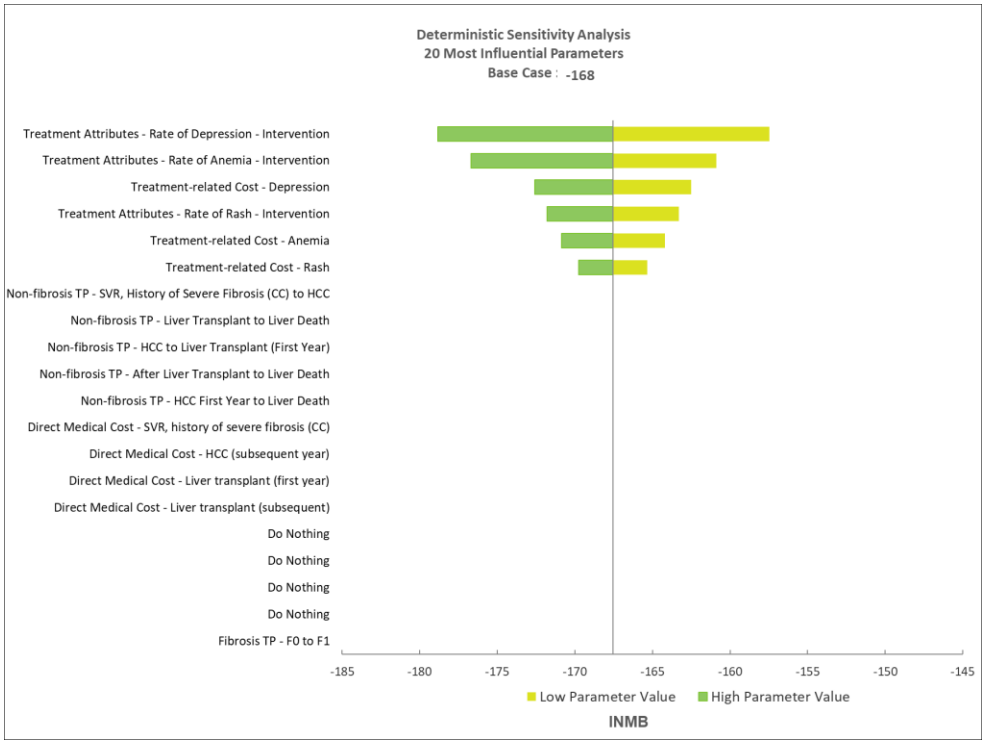
Source: response to clarification letter Appendix F.[17]

Figure A.6: Tornado diagram: GT2 TN NC IFN-ineligible, G/P vs. SOF + RBV



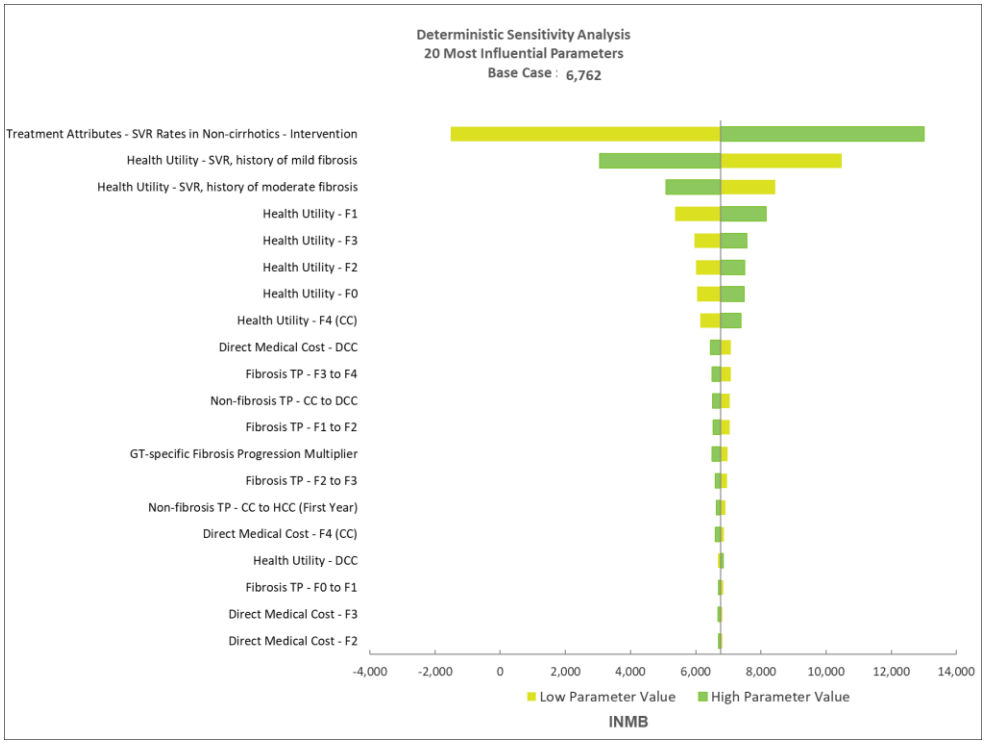
Source: response to clarification letter Appendix F.[17]

Figure A.7: Tornado diagram: GT2 TN CC, G/P vs. SOF/VEL[a]



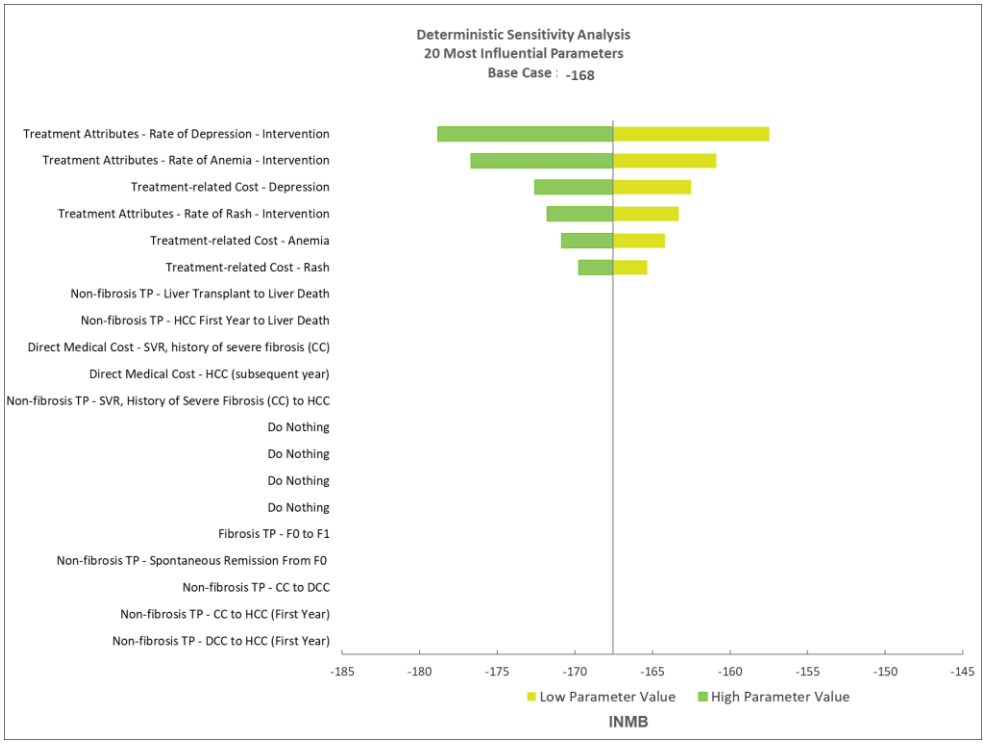
[a]As the comparator for DSA is the same in the GT2 TN CC IFN-eligible and IFN-ineligible subgroups, and there are no differences between the modelling of these two subgroups, the above tornado diagram applies to both groups. Source: response to clarification letter Appendix F.[17]

Figure A.8: Tornado diagram: GT2 TE NC, G/P vs. SOF/VEL



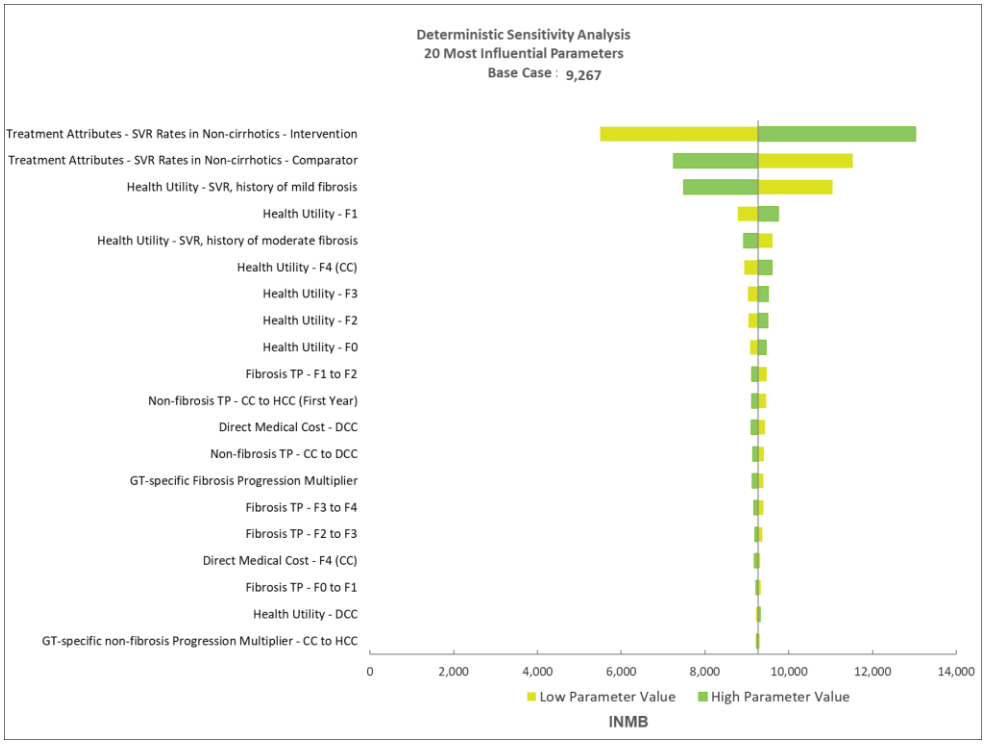
Source: response to clarification letter Appendix F.[17]

Figure A.9: Tornado diagram: GT2 TE CC, G/P vs. SOF/VEL



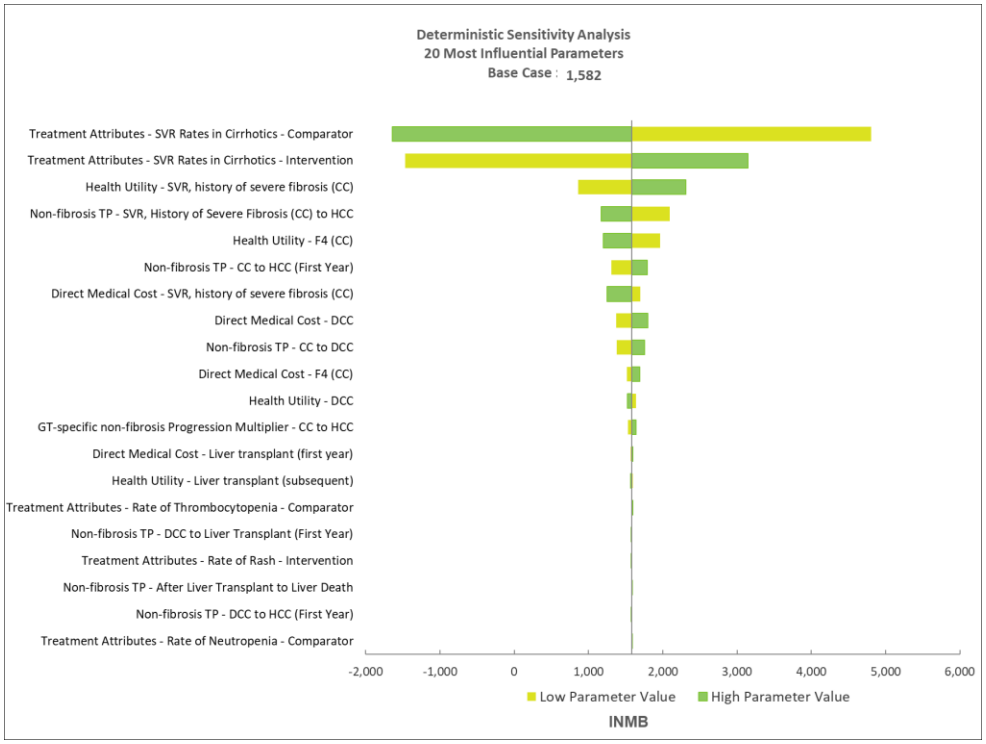
Source: response to clarification letter Appendix F.[17]

Figure A.10: Tornado diagram: GT3 TN NC, G/P vs. SOF/VEL



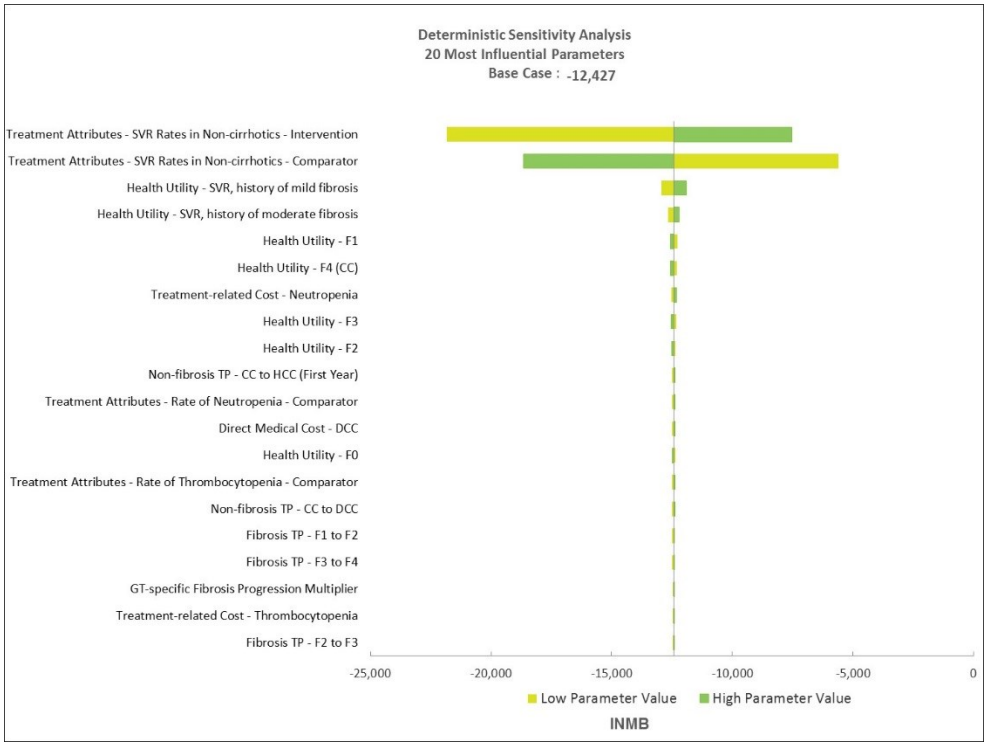
Source: response to clarification letter Appendix F.[17]

Figure A.11: Tornado diagram: GT3 TN CC, G/P vs. SOF/VEL



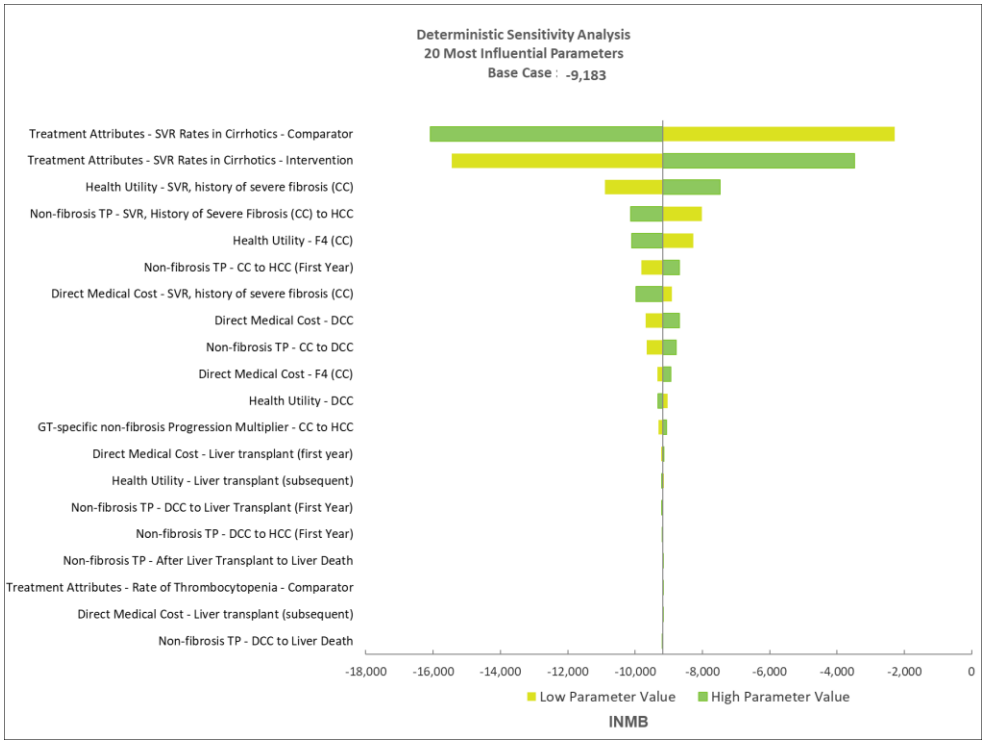
Source: response to clarification letter Appendix F.[17]

Figure A.12: Tornado diagram: GT3 TE NC, G/P vs. SOF + peg-IFN + RBV



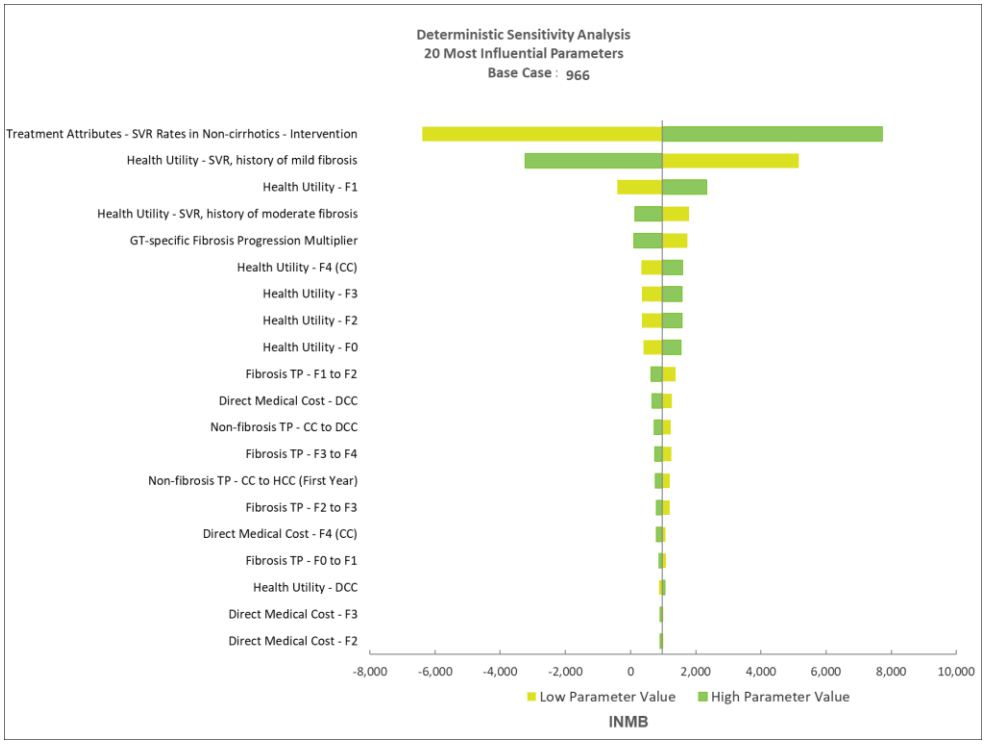
Source: Electronic model.[204]

Figure A.13: Tornado diagram: GT3 TE CC, G/P vs. SOF/VEL



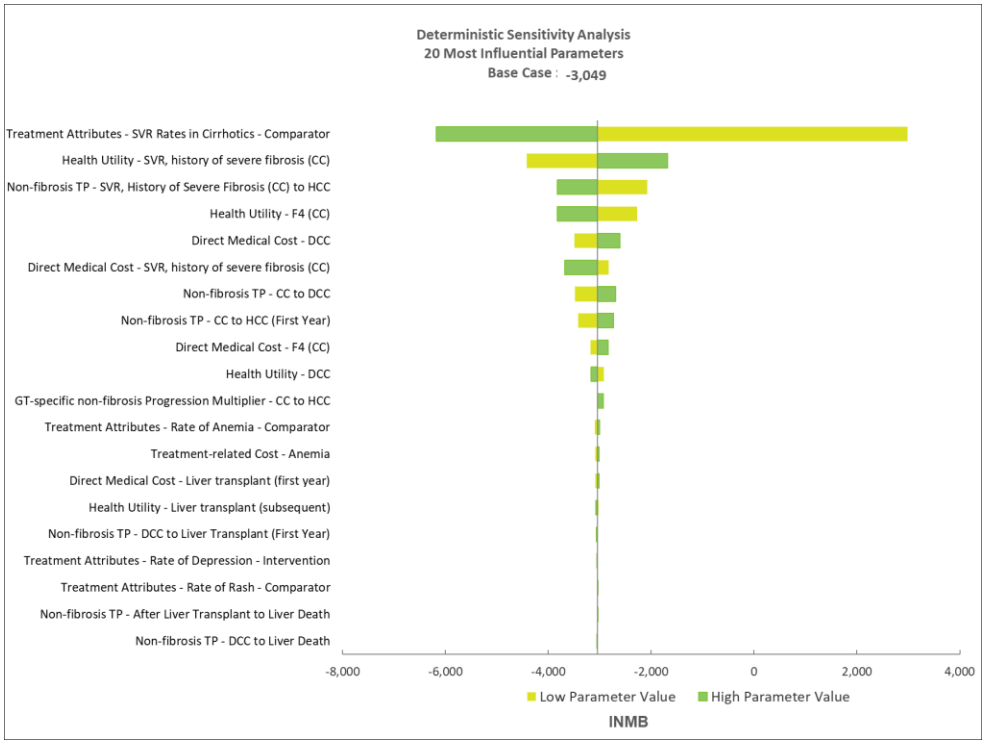
Source: response to clarification letter Appendix F.[17]

Figure A.14: Tornado diagram: GT4 TN NC, G/P vs. OBV/PTV/RTV



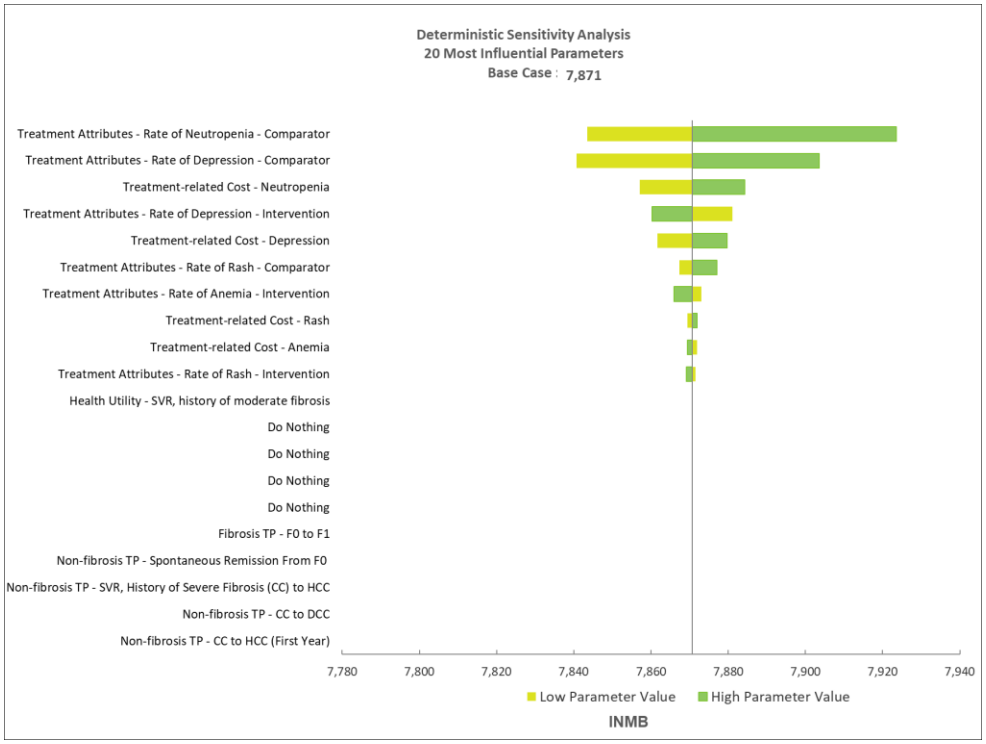
Source: response to clarification letter Appendix F.[17]

Figure A.15: Tornado diagram: GT4 TN CC, G/P vs. OBV/PTV/RTV



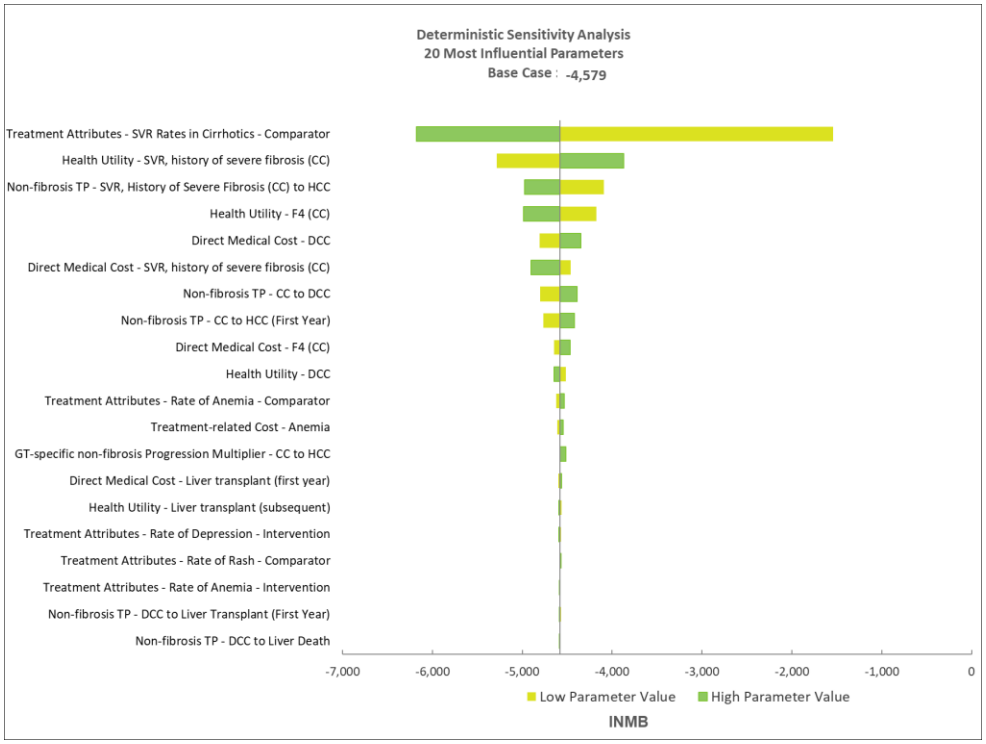
Source: response to clarification letter Appendix F.[17]

Figure A.16: Tornado diagram: GT4 TE NC, G/P vs. OBV/PTV/RTV



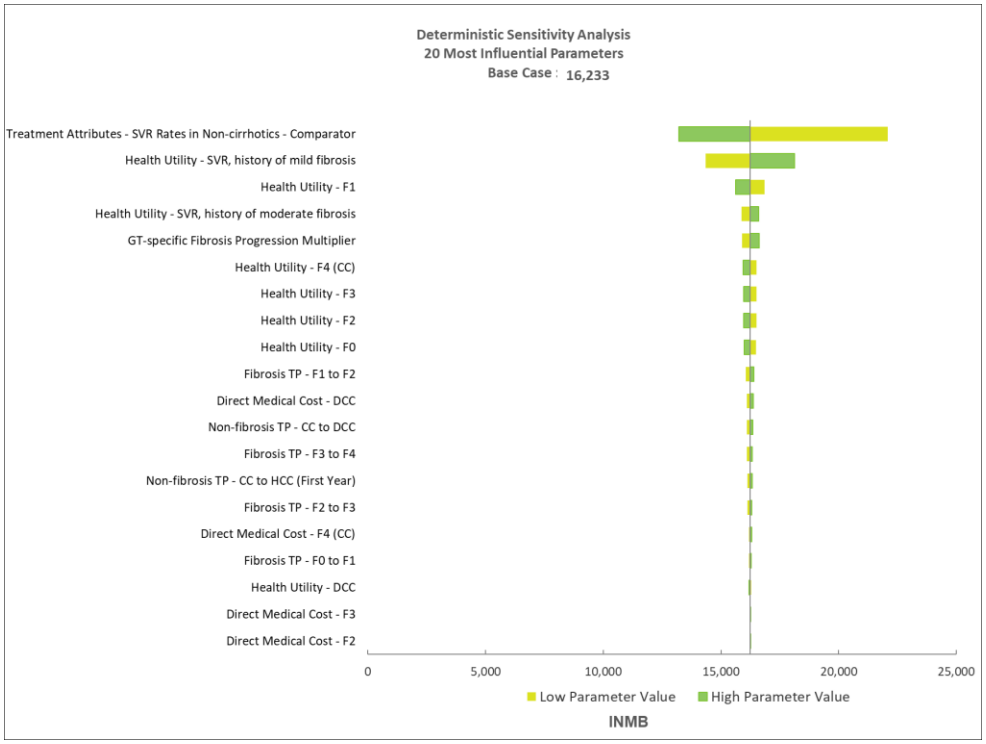
Source: response to clarification letter Appendix F.[17]

Figure A.17: Tornado diagram: GT4 TE CC, G/P vs. OBV/PTV/RTV



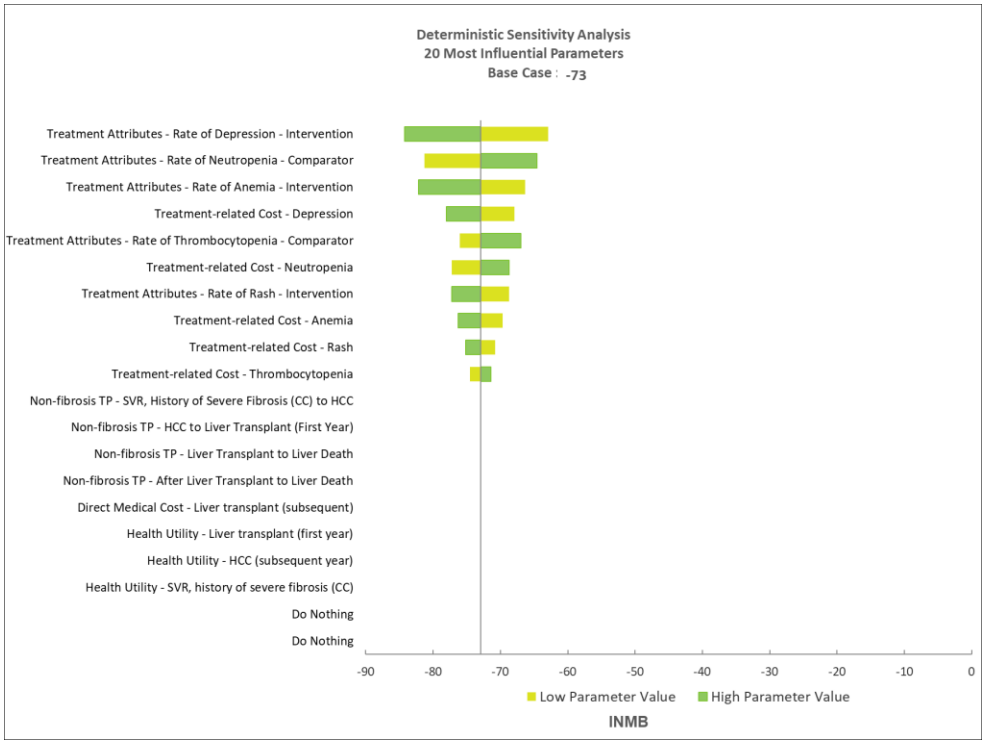
Source: response to clarification letter Appendix F.[17]

Figure A.18: Tornado diagram: GT5 TN NC, G/P vs. SOF/VEL



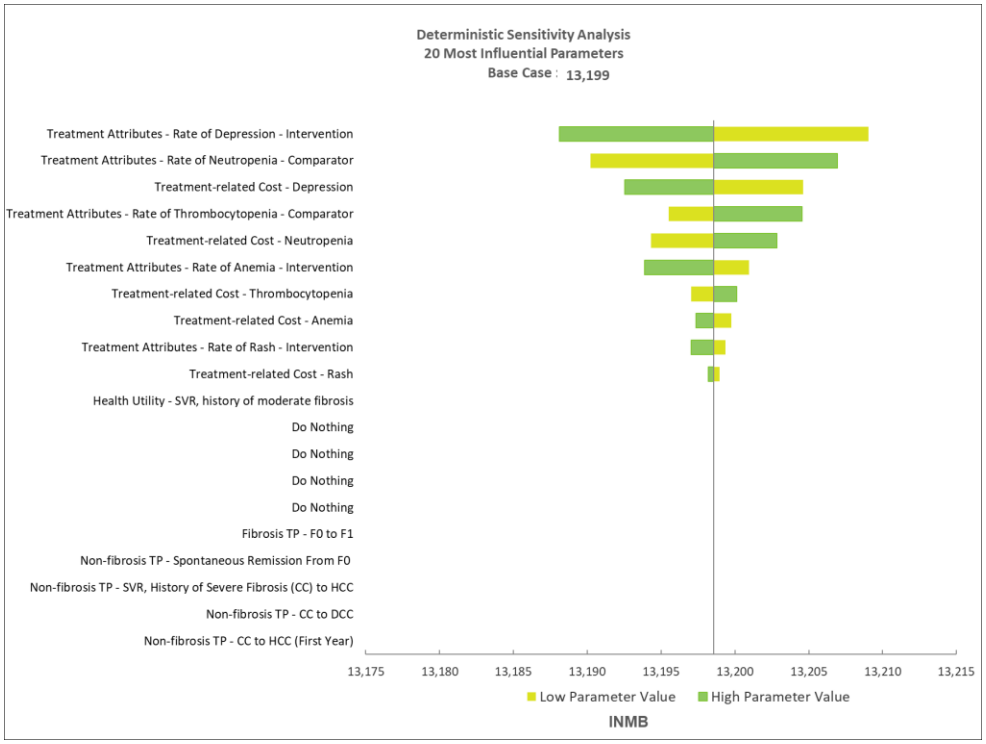
Source: response to clarification letter Appendix F.[17]

Figure A.19: Tornado diagram: GT5 TN CC, G/P vs. SOF/VEL



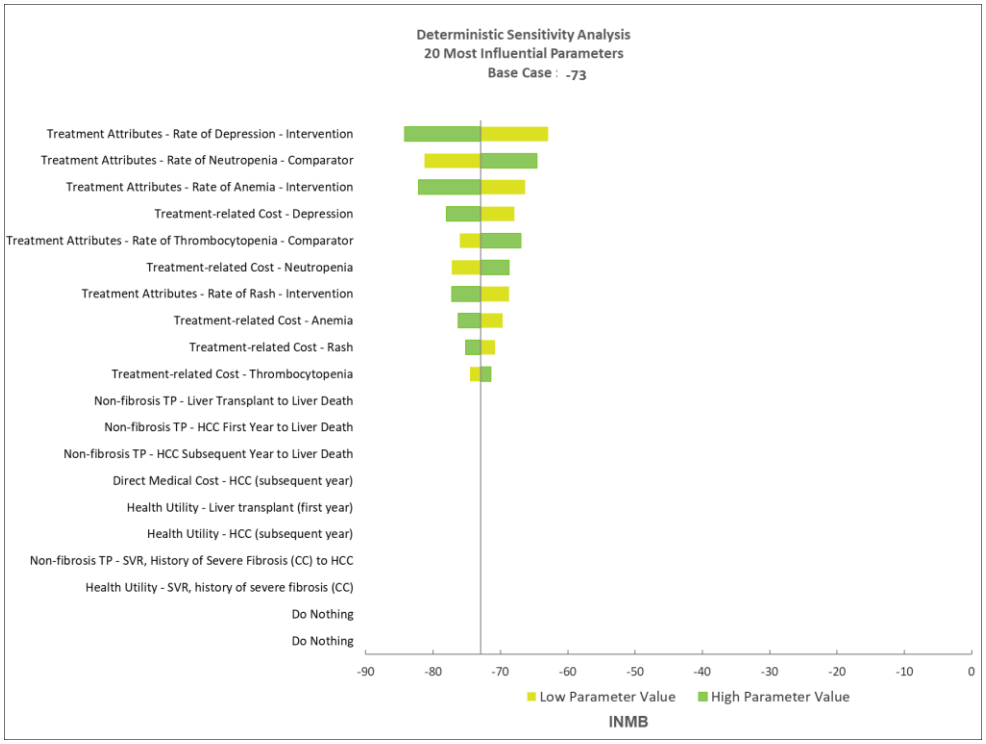
Source: response to clarification letter Appendix F.[17]

Figure A.20: Tornado diagram: GT5 TE NC, G/P vs. SOF/VEL



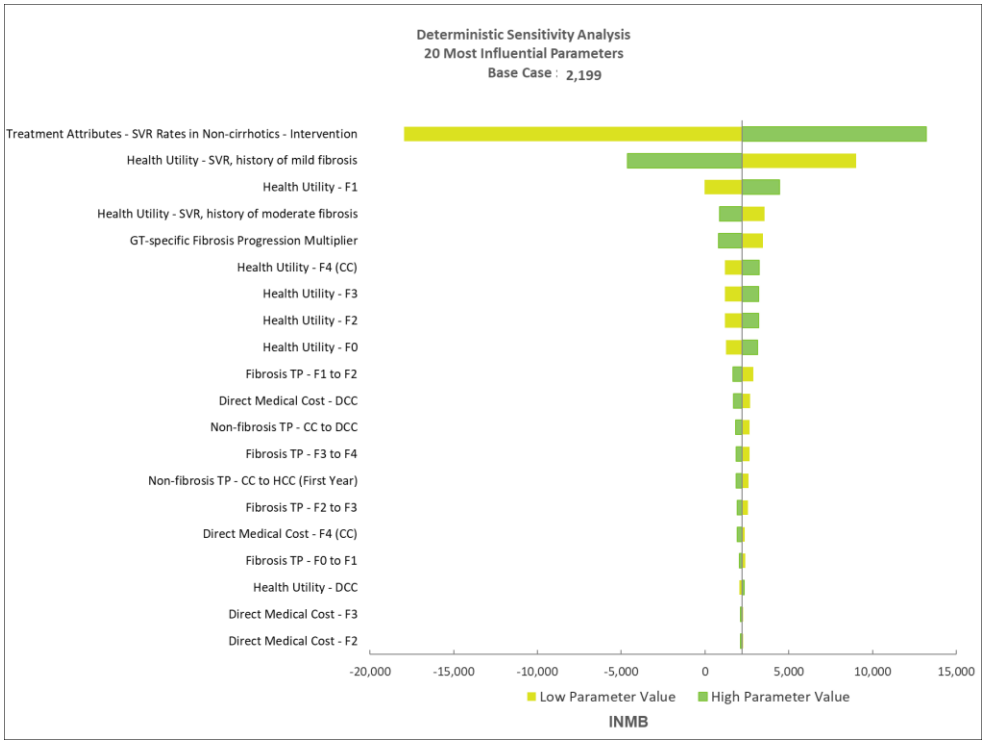
Source: response to clarification letter Appendix F.[17]

Figure A.21: Tornado diagram: GT5 TE CC, G/P vs. SOF/VEL



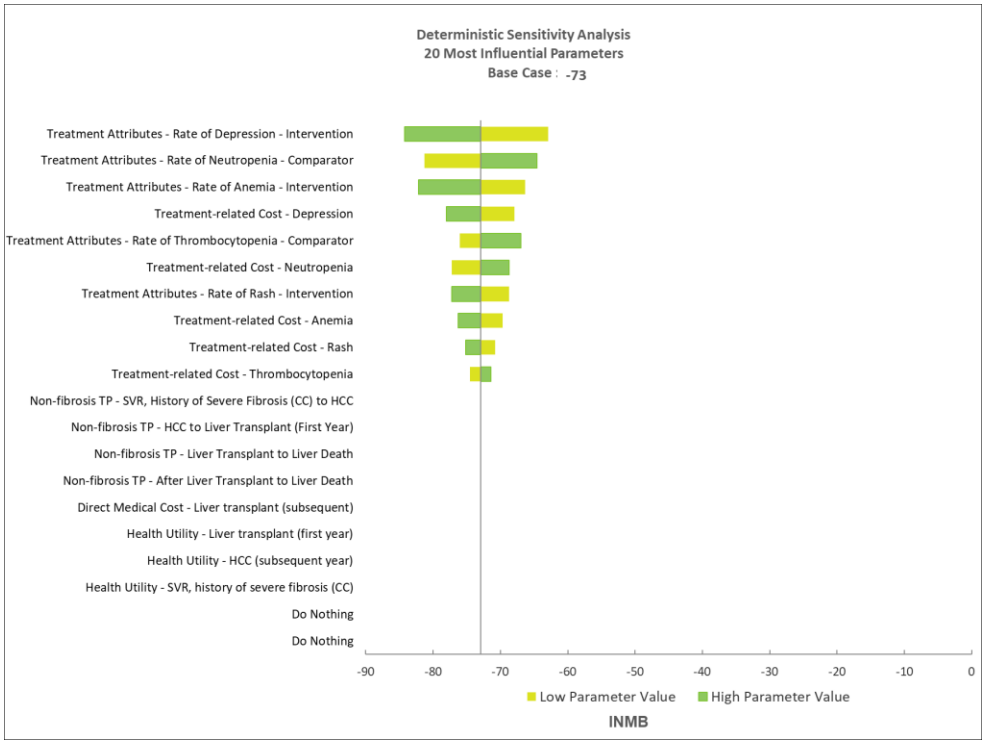
Source: response to clarification letter Appendix F.[17]

Figure A.22: Tornado diagram: GT6 TN NC, G/P vs. SOF/VEL



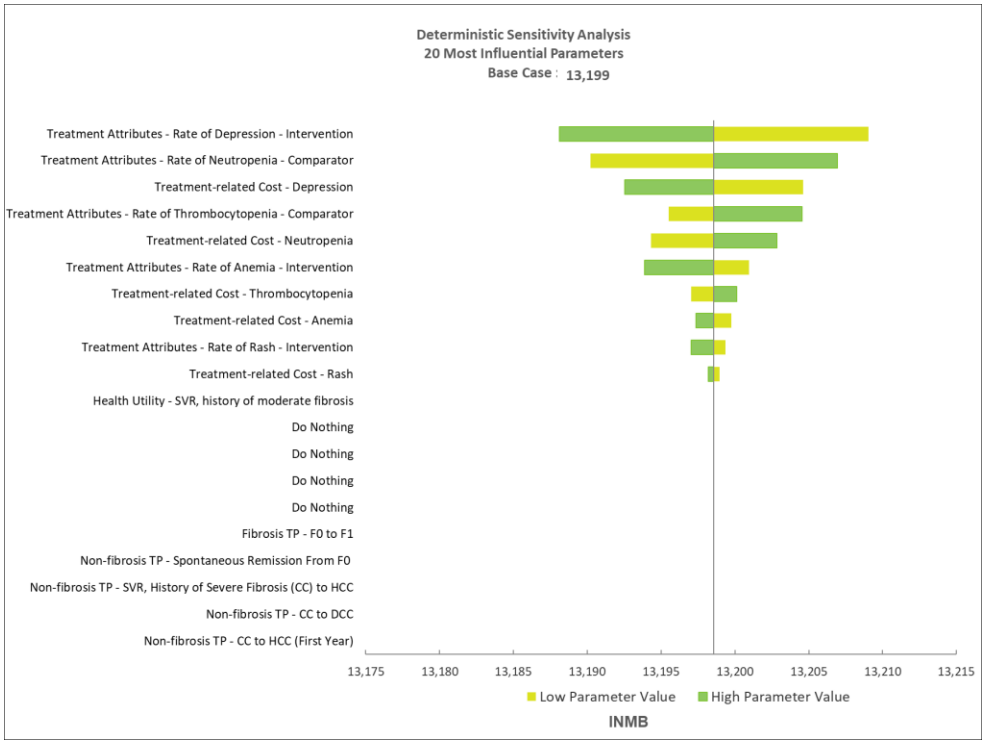
Source: response to clarification letter Appendix F.[17]

Figure A.23: Tornado diagram: GT6 TN CC, G/P vs. SOF/VEL



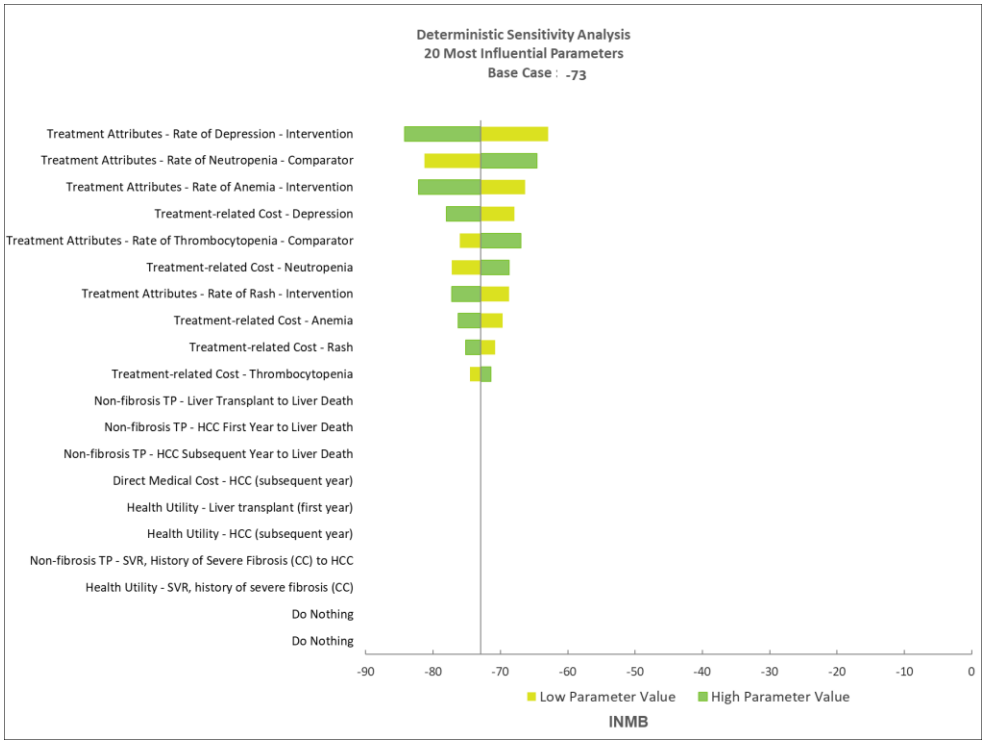
Source: response to clarification letter Appendix F.[17]

Figure A.24: Tornado diagram: GT6 TE NC, G/P vs. SOF/VEL



Source: response to clarification letter Appendix F.[17]

Figure A.25: Tornado diagram: GT6 TE CC, G/P vs. SOF/VEL



Source: response to clarification letter Appendix F.[17]

Table A.27: Non-treatment-specific input parameters included in the probabilistic sensitivity analysis

Parameter	Base value	Low	High	Standard error	Distribution
Transitional probabilities (annual)					
GT1 fibrosis progression					
F0–F1	0.110	0.088	0.132	0.011	BETA
F1–F2	0.088	0.070	0.105	0.009	BETA
F2–F3	0.176	0.141	0.211	0.018	BETA
F3–CC	0.143	0.114	0.172	0.014	BETA
GT-specific fibrosis progression multiplier					
GT2	0.68	0.64	0.73	0.026	NORMAL
GT3	1.30	1.22	1.39	0.046	NORMAL
GT4	0.94	0.78	1.14	0.102	NORMAL
GT5	0.94	0.78	1.14	0.102	NORMAL
GT6	0.94	0.78	1.14	0.102	NORMAL
Non-fibrosis disease progression					
SVR, history of CC (F4) to HCC	0.012	0.003	0.022	0.011	BETA
CC to DCC	0.039	0.029	0.049	0.010	BETA
CC to HCC	0.014	0.004	0.024	0.010	BETA
LT					
DCC to LT (first year)	0.020	0.016	0.024	0.002	BETA
HCC to LT (first year)	0.020	0.016	0.024	0.002	BETA
Liver-related mortality					
DCC to liver death	0.130	0.120	0.140	0.010	BETA
LT (first year) to liver death	0.150	0.120	0.180	0.015	BETA
LT (subsequent year) to liver death	0.057	0.046	0.068	0.006	BETA
HCC to liver death	0.430	0.400	0.460	0.030	BETA
GT-specific non-fibrosis transition rate multipliers					
CC to HCC multiplier					
GT2	0.62	0.50	0.77	0.077	NORMAL
GT3	1.44	1.23	1.68	0.122	NORMAL
GT4	0.96	0.96	1.22	0.133	NORMAL
GT5	0.96	0.96	1.22	0.133	NORMAL
GT6	0.96	0.96	1.22	0.133	NORMAL
DCC to HCC multiplier					
GT2	0.62	0.50	0.77	0.077	NORMAL

Parameter	Base value	Low	High	Standard error	Distribution
GT3	1.44	1.23	1.68	0.122	NORMAL
GT4	0.96	0.96	1.22	0.133	NORMAL
GT5	0.96	0.96	1.22	0.133	NORMAL
GT6	0.96	0.96	1.22	0.133	NORMAL
Health state utilities[a]					
F0	0.77	0.62	0.92	0.077	BETA
F1	0.77	0.62	0.92		
F2	-0.11	-0.18	-0.04	0.035	LOG-NORMAL
F3	0.66	0.53	0.79		
CC (F4)	-0.22	-0.30	-0.13	0.043	LOG-NORMAL
SVR, history of mild fibrosis (F0, F1)	0.82	0.66	0.98		
SVR, history of moderate fibrosis (F2, F3)	0.71	0.57	0.85		
SVR, history of CC	0.60	0.48	0.72		
DCC	0.45	0.36	0.54	0.045	BETA
HCC	0.45	0.36	0.54	0.045	BETA
LT (first year)	0.45	0.36	0.54	0.045	BETA
LT (subsequent)	0.67	0.54	0.80	0.067	BETA
Health state costs (2015/2016 £)[b]					
F0	164	82	246	45	GAMMA
F1	164	82	246	45	GAMMA
F2	609	431	861	100	GAMMA
F3	609	431	861	100	GAMMA
CC (F4)	945	579	1,541	220	GAMMA
SVR, history of mild fibrosis (F0–F1)	60	47	78	10	GAMMA
SVR, history of moderate fibrosis (F2–F3)	60	47	78	10	GAMMA
SVR, history of CC (F4)	606	214	1,711	300	GAMMA
DCC	12,670	6,335	19,006	3,200	GAMMA
HCC	11,291	5,645	16,936	3,100	GAMMA
LT (first year)	51,108	25,554	76,662	13,000	GAMMA
LT (subsequent year)	1,924	962	2,886	500	GAMMA
Treatment-related AE costs (2015/2016 £)[b]					
Anaemia	486	243	729	150	GAMMA
Rash	160	80	240	40	GAMMA
Depression	490	245	735	150	GAMMA

Parameter	Base value	Low	High	Standard error	Distribution
Grade 3/4 neutropaenia	1,334	667	2,001	330	GAMMA
Grade 3/4 thrombocytopoenia	1,902	951	2,854	475	GAMMA

Source: Table 233 in Appendix L.1.2 in the CS.[16]
[a]1. Health utilities from Wright et al. (2006)[153] combine F0 and F1 into mild and F2 and F3 into moderate. Therefore, health utilities for F0 is drawn and used for F0 and F1 and health utilities for F2 is drawn and used for F2 and F3. 2. For moderate (F2) and F4, the Base/Low/High columns correspond to the difference vs. mild per Table 50 of Wright et al. (2006). One exception: the mean difference between mild and CC was reported as -0.21 whereas the difference between mild (0.77) and CC (0.55) is in fact -0.22. This is likely due to rounding issue. The correction has been made here for consistency. 3. Moderate (F2) and CC (F4) are not sampled from a Beta distribution. Rather, the relative difference (delta or ratio) between moderate/CC and mild was sampled from the log-normal distribution which was applied to obtain health utilities in moderate and CC at each simulation. 4. Recovered states are not sampled from a beta distribution. Rather, a fixed +0.05 increase (base-case value) from the initial fibrosis stage is assumed; [b]Gamma: Each standard error has been selected such that the 95% CI obtained through 500 simulations replicates as closely as possible the lower and upper bound of the parameter in question. 5. No HCV state is not sampled from a Beta distribution. Rather, the drawn value for SVR history of mild fibrosis is used (base-case assumption).
AE, adverse event; CC, compensated cirrhosis; CI, confidence interval; DCC, decompensated cirrhosis; DSA, deterministic sensitivity analysis; GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; N/A: Not applicable; PSA, probabilistic sensitivity analysis; SVR, sustained virologic response

Probabilistic sensitivity analysis - results at £30,000 threshold

Table A.28: G/P cost effectiveness probability (%) at £30,000 threshold (against the indicated comparator)

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	99.2% (SOF/LDV)	71.0% (EBR/GZR)	100% (OBV/PTV/RTV + DSV)	13.4% (SOF/VEL)
GT2	IFN-eligible: 36.6% (peg-IFN + RBV)	IFN-eligible: 45.5% (SOF/VEL)	93.4% (SOF/VEL)	41.2% (SOF/VEL)
	IFN-ineligible: 100% (SOF + RBV)	IFN-ineligible: 45.5% (SOF/VEL)		
GT3	99% (SOF/VEL)	74.4% (SOF/VEL)	0.0% (SOF + peg-IFN + RBV)	4.4% (SOF/VEL)
GT4	41.0% (OBV/PTV/RTV)	23.8% (OBV/PTV/RTV)	100% (OBV/PTV/RTV)	6.2% (OBV/PTV/RTV)
GT5	100% (SOF/VEL)	49.6% (SOF/VEL)	100% (SOF/VEL)	39.4% (SOF/VEL)
GT6	55.4% (SOF/VEL)	47.0% (SOF/VEL)	100% (SOF/VEL)	46.8% (SOF/VEL)

Source: Table 53 in the CS.[2]
DSV = dasabuvir; EBR = elbasvir; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; PSA = probabilistic sensitivity analysis; PTV = paritaprevir; peg-IFN = pegylated IFN; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; VEL = velpatasvir

Table A.29: G/P cost effectiveness probability (%) at £30,000 threshold for patients with compensated cirrhosis in the company submission (against only one comparator) and with multiple comparators

HCV genotype	Treatment-naïve		Treatment-experienced	
	One comparator*	All comparators**	One comparator*	All comparators**
GT1	71.0%	57.8%	13.4%	11.2%
GT2	IFN-eligible*: 45.5%	IFN-eligible: 43.0%	41.2%	41.4%
	IFN-ineligible*: 45.5%	IFN-ineligible: 45.2%		
GT3	74.4%	64.4%	4.4%	7.6%
GT4	23.8%	4.2%	6.2%	5.2%
GT5	49.6%	47.4%	39.4%	42.4%

GT6	47.0%	48.2%	46.8%	44.8%

GT = genotype; IFN = interferon
*Comparators in Table 5.18. **Comparators in Table 5.6.
Note: shaded cells indicate a difference of at least 10% in the cost effectiveness probability of G/P vs. one or all relevant comparators for each subgroup.

Table A.30: G/P cost effectiveness probability (%) at £30,000 threshold (against all comparators and including 100% SVR rates and 0% AE rates in the PSA)

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	100%	60.8%	100%	3.8%
GT2	IFN-eligible: 38.8%	IFN-eligible: 58.0%	95.8%	63.2%
	IFN-ineligible: 100%	IFN-ineligible: 50.4%		
GT3	98.4%	61.0%	0.0%	3.8%
GT4	40.0%	11.2%	61.6%	2.8%
GT5	26.2%	27.2%	95.4%	20.4%
GT6	26.0%	47.8%	80.2%	39.8%

Source: Electronic model.[204]
GT = genotype; IFN = interferon; PSA = probabilistic sensitivity analysis

AbbVie Ltd
AbbVie House
Vanwall Business Park
Maidenhead
SL6 4UB

Helen Knight
Level 1A City Tower
Manchester
M1 4BT

16th October 2017

Dear Helen,

Glecaprevir with pibrentasvir (G/P) (Maviret) for treating HCV [ID1085] – Response to ERG Report

Thank you for providing the ERG report for fact checking. The NICE proforma document for detailing factual inaccuracies has been completed and is presented at the end of this letter. There are a number of points repeated throughout the ERG report which are either factually inaccurate or potentially misleading without the appropriate context and these are detailed below:

1. The NHS Commissioning Medicines Unit (CMU) has now accepted the pricing agreement for glecaprevir-pibrentasvir (Maviret®) (The ERG was informed of this development during the clarification call and in the letter accompanying the response to clarification questions). The confidential agreement offers a [redacted] In the ERG report only list price base-case cost effectiveness (and probabilistic sensitivity analyses) results are presented. However list price results are not relevant for decision making since G/P and many comparators have had confidential discounted prices agreed. NICE confirmed that the ERG has conducted analyses using the Maviret (G/P) CMU price and relevant comparator discounted prices and that these will be presented to the appraisal committee as a confidential addendum. In the interest of transparency and to avoid misleading the public, the existence of a confidential addendum incorporating discounted prices should be stated in all sections that discuss the results of list price comparisons. The irrelevance of list price base case results to decision making should also be discussed.
   ERG RESPONSE: This is the way NICE asked us to write the report.
2. Sections of the ERG report, which currently mention the CHMP opinion need to be updated to reflect the latest G/P regulatory update: that on 26th July 2017, the European Commission granted glecaprevir/pibrentasvir (Maviret®) marketing authorisation for the treatment of chronic hepatitis C in all major genotypes (GT1 -6).
   ERG RESPONSE: Not a factual error. The information in the ERG report is correct and the marketing authorisation is in line with the original CHMP opinion.
3. The ERG's critique of the company submission could be misinterpreted if not read in its entirety since important contextualising text tends to have been included as just a sentence at the end of pages of critique, rather than in tandem. For example:
   - The ERG extensively critiques the absence of a number of comparators and then mentions (pages 23 and 32) that the clinical expert they consulted supported the company's position: *"**The ERG's clinical expert agreed that indeed these treatment regimens were no longer used in NHS clinical practice**".*
   - Similarly, the commentary on the robustness of the evidence submitted by the company, in the main part of the ERG report is long and detailed but omits an important context, which is once again only presented towards the end (section 6, page 132): that "*the ERG has not presented an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, **as in most situations the assumptions made by the company were reasonable and in line with previous appraisals**"*
   - The ERG report critiques the absence of development of resistance to G/P and comparator treatment in the economic model, but then later on (pg 32) states that "*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.

- The ERG critiques the absence of a formal indirect comparison in the company submission but then later states (page 75): "*Although* ***the ERG agrees that it is not feasible to form any network between G/P and any relevant comparator therapies and that the limited availability of baseline characteristics for comparator studies precludes an adjusted analysis****, it should be taken into account that the results of these naïve indirect comparisons are unreliable"*

We would recommend incorporating the ERG's contextualising comments in tandem with the critique of the company submission in order to avoid inadvertent misrepresentation.
ERG RESPONSE: Not a factual error.

4. Finally many of the limitations highlighted by the ERG (e.g. single arm trial design and the use of naive indirect comparisons in the economic model) are inherent in the HCV disease area as has been noted in previous technology appraisals such as TA430, all of which have been recommended for use in the NHS. We recommend highlighting this important context at the outset.
   ERG RESPONSE: Not a factual error. It is our remit to point out the uncertainties in the companies submission.

Thank you for your time and please do not hesitate to contact me using the details below if you would like to discuss further.

Yours sincerely,

[redacted]

[redacted]

PHONE [redacted]
EMAIL [redacted]

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Glecaprevir with pibrentasvir for treating chronic hepatitis C [ID1085]

You are asked to check the ERG report from Kleijnen Systematic Reviews Ltd to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 16 October 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 14 sentence: 'The company's model does not include the development of resistance to G/P and other comparators based on the assumption that this outcome does not impact the cost effectiveness of G/P.' This critique should include the context, provided later on p. 31, that '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' which justifies the absence of development of resistance to treatment in the company model.	Amend to: ''The company's model does not include the development of resistance to G/P and other comparators based on the assumption that this outcome does not impact the cost effectiveness of G/P; the clinical advice received by the ERG was that this outcome is less relevant.'	The ERG report unfairly criticises the model for an assumption that is deemed reasonable by clinical experts who advised the ERG.	Not a factual error, the information in the ERG report is correct.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 14 sentence '[redacted]' has no confidentiality marking. This is repeated on p. 54 (Section 4.2.2) and p. 133 (Section 7.1)	This sentence should be marked as academic in confidence.	The information reported in this sentence has not been published.	AiC has been added.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 15: 'Additional searches of conference proceedings were conducted but no separate literature searches were undertaken to	Amend to: 'Additional searches of conference proceedings were	This statement in the ERG report is confusing, and is	Not a factual error.

identify adverse events data, non-randomised and non-controlled evidence.' There are two issues to raise. This sentence should be split in two as per the proposed amendment, as it concerns two points: 1) additional searches of conference proceedings were conducted. 2) No separate literature searches were undertaken to identify adverse events data, non-randomised and non-controlled evidence. The second point is misleading. The clinical efficacy SLR was conducted in line with NICE user guide for the company evidence submission, and this SLR incorporated searches for adverse events data, non-randomised and non-controlled evidence. This is evidenced by the fact that the majority of the clinical evidence in the submission is derived from non-randomised and non-controlled trials.	conducted. No separate literature searches were undertaken to identify adverse events data, non-randomised and non-controlled evidence because these searches were incorporated in the main clinical efficacy SLR.	factually inaccurate as it fails to acknowledge the scope of the clinical efficacy SLR that was conducted by the company.	Guidance by the Centre for Reviews and Dissemination (CRD) 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. As the clinical effectiveness searches were undertaken with study design filters or in study design specific resources, it is possible that some relevant evidence was not identified as a consequence.

Issue 4

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
P. 15 sentence 'Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC)' is inaccurate. For GT3/TN/NC, ENDURANCE-3 studied 8 weeks of G/P (the licensed dose for this subgroup) in 157 patients and therefore should be included in this list. This is also repeated several times elsewhere in the ERG report (p. 18, p, 54, p. 58, p. 93, p. 134) and should be amended throughout. The sentence should also acknowledge the low prevalence of GT4–6, which is a barrier to having patient numbers >100 with those genotypes in clinical trials. Notably, G/P has a somewhat	This sentence should read: 'Four out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC, GT2/TN/NC, GT3 TN/NC); GT4–6 have much lower prevalence in the population, likewise most patients across GTs are both TN and NC.'	As stated, for GT3/TN/NC, ENDURANCE-3 studied 8 weeks of G/P (the licensed dose for this subgroup) in 157 patients and therefore should be included in this list. Furthermore, as explained, due to the prevalence of specific GTs and the fact that the majority of patients are TN NC, these factors create limitations to number of patients in several subgroups	We corrected the statement that four instead of three of the 24 subgroups included more than 100 patients. The other comments do not refer to factual errors.

larger evidence base in GT4–6 compared to sofosbuvir/velpatasvir (SOF/VEL), the only other pan-genotypic treatment considered by NICE: G/P's Phase 2 and 3 clinical trial programme presented in the company submission enrolled 288 GT4–6 patients, whereas SOF/VEL's Phase 3 trials recently considered NICE enrolled 208 GT4–6 patients. The sentence ought also to acknowledge that the majority of patients are TN and NC, so recruiting high number of TE or CC patients is challenging. The use of the word 'only' implies that these limitations were due to the trials rather than inherent to the epidemiology of the disease.		that can realistically be recruited to clinical trials. This is reflected in the number of patients recruited to clinical studies for comparator treatments, such as SOF/VEL.	

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 15 sentence 'Therefore, the uncertainty around SVR rates in most subgroups is considerable.' This statement does not reference a quantification of the extent of uncertainty. This statement is repeated elsewhere in the ERG report e.g. p. 18, p. 54, p. 78, p. 93, p. 134, and should be amended whenever it is repeated.	Change to: 'Therefore there is uncertainty around SVR rates in most subgroups.'	The proposed amendment is more accurate given that there is no quantification of the extent of uncertainty in this context, so there is no evidence supporting describing it as 'considerable.'	Not a factual error.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 15 sentence 'The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used.'	The ERG report should amend this to acknowledge the selection methodology described in the response to ERG clarification question A28.	The response to ERG clarification question A28 systematically described how SVR and AE data were drawn for comparators.	Not a factual error. In Question A28 the company describes the numbers taken from individual studies. However, in the CS (page 156)

The statement about how response and adverse events for comparator studies were selected and whether all possible sources were used is inaccurate, as the method of selection was explained in the response to ERG clarification question A28. This statement is repeated elsewhere in the ERG report e.g. p. 18, p. 78, p. 93, p. 134 and should be amended whenever it is repeated.			the company stated "For comparator interventions that were also included in the model submitted in TA430,[1] the same sources for SVR rates were used for this model and the TA430 model, with the exceptions described in Table 64." Therefore, in most cases the critique from TA430 applies that 'The company does not present any information about how response and adverse events for comparator studies were selected and whether all possible sources were used.'

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 15 sentence: 'In most cases the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.' If SVR rates were the same as used in TA430, then this means that the SVR rates were based on an accepted historical precedent rather random selection or 'cherry-picking.' This statement is repeated elsewhere in the ERG report e.g.	The ERG report should acknowledge that the SVR and AE rate sources were based on accepted historical precedent. The sentence should be amended to: "In most cases the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Consistency with the previous NICE TA430 avoids introducing new bias or cherry-picking given the constraints of	The company submission justified why naïve indirect comparisons were necessary as inputs for the economic model. The company based the inputs for the economic model on the most recent NICE submission, considering that using this historically accepted precedent as the best method of selecting inputs in an un-biased manner as	Not a factual error. If the company used the same methods, then the same critique applies as for TA430.

p. 18, p. 75, p. 78, p. 134 and should be amended whenever it is repeated.	the available evidence."	possible. The ERG report does not acknowledge that this was the most reasonable approach given the constraints of the available evidence.	

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 15 sentence: 'The population considered in the cost effectiveness analyses was sub-divided into 26 different subgroups, where patients were stratified by genotypes (GT1, GT2, GT3, GT4, GT5 and GT6), treatment experience (treatment-naïve and treatment-experienced patients), cirrhosis status (cirrhotic and non-cirrhotic patients) and IFN-eligibility (only for GT2 TN patients).' It is not made clear that the cost effectiveness analysis subgroups with cirrhosis had ***compensated*** cirrhosis in line with the license for G/P. Throughout the ERG report this distinction is not made, and this ambiguity is not in line with the license for G/P.	Throughout the report **each and every** instance of 'cirrhosis' in the context of the licensed cirrhotic population for G/P (including any discussion of economic subgroups) must be clarified with the addition of the word 'compensated.'	The company submission made clear in every instance that the licensed cirrhotic population for G/P is those patients with compensated cirrhosis only, and this should be reflected in the ERG report. Nothing in the company submission or in this appraisal will consider patients with decompensated cirrhosis who are outwith the licensed indication.	Not a factual error. It is clearly stated in the ERG report that "The G/P studies included patients with all genotypes; treatment-naïve and treatment-experienced patient populations; and patients with 'no cirrhosis or compensated cirrhosis'" (ERG report, page 14). At the start of the economic section this is repeated: "The model assumes that all cirrhotic patients in the treatment phase have compensated cirrhosis (CC). This is because G/P is not licensed for use in patients with decompensated cirrhosis (DCC)." (ERG report, page 86).

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 16 sentence 'List prices were used as treatment costs for G/P and the comparator treatments in the cost effectiveness analysis.' This is factually inaccurate by omission of discussion of the results of the pricing scenario analysis, which used the accepted CMU price for G/P. In considering the list price results it should be noted that several comparators have PAS price agreements; combined with the fact that the CMU price for G/P has been agreed, the list prices used in the base-case are not a realistic representation of the cost-effectiveness of G/P. Without this context, the list-price results are misleading and a misrepresentation of the cost-effectiveness of G/P in practice to NHS England. This was acknowledged in the ERG report for Epclusa (TA430) as follows: 'The ERG thinks that the cost effectiveness analysis based on list prices may not reflect the actual value for money of the HCV treatments' (p. 12). This is repeated on p. 129 and should be amended appropriately there as well.	The ERG report should describe how the list price base case results are not representative of the cost-effectiveness of G/P due to the agreed CMU price; the report should focus the discussion on the results of the pricing scenario analysis, which are a more realistic representation, and reference that these were supplied in Appendix L.1.4 of the company submission and subsequently updated in response to ERG clarification B14. Whenever list price results are discussed, or the conclusions from the list price results are described, this context and the results of the pricing scenario analysis should also be discussed. Statements such as 'when the analyses were run using the agreed GPCMU price, which reflects the real discounted price to the NHS, GP was cost-effective in all subgroups' could be added without confidentiality marking, enabling the report to be transparent without revealing the level of discount for GP or for any comparators.	Without the context of the existence of PAS and CMU pricing agreements, the discussion of the list price results in isolation is a misrepresentation of the cost-effectiveness of G/P in practice to NHS England. The ERG report for the NICE appraisal of the only other pan-genotypic regimen in this therapy area – Epclusa, TA430) – reported this context, and it is misleading to omit this from the ERG report for the appraisal of G/P.	Not a factual error. This was requested by NICE and is normal practice in ERG reports.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 16 sentence 'For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).' As discussed in Issue 9, the reporting of these results lacks the context that results using list prices are not representative of the true cost-effectiveness of G/P, as similarly acknowledged in the ERG report for Epclusa (TA430), due to the existence of PAS agreements for comparators and the CMU pricing agreement for G/P. This context should be described whenever list-price results are reported, e.g. p. 113 and p. 133-134, and the results of the pricing analysis reported in the same place.	This reporting of the economic analysis results should include the pricing scenario results, which were supplied in Appendix L.1.4 of the company submission and subsequently updated in response to ERG clarification B14, because the list price results are not the basis for decision making and are not representative of the cost-effectiveness of G/P to NHS England. As described in Issue 9, statements such as 'when the analyses were run using the agreed GP CMU price, which reflects the real discounted price to the NHS, GP was cost-effective in all subgroups' could be added without confidentiality marking, enabling the report to be transparent without revealing the level of discount.	Without the context of the existence of PAS and CMU pricing agreements, the discussion of the list price results in isolation is a misrepresentation of the cost-effectiveness of G/P in practice to NHS England. The ERG report for the NICE appraisal of the only other pan-genotypic regimen in this therapy area – Epclusa, TA430) – reported this, and it is misleading to omit this from the ERG report for the appraisal of G/P.	Not a factual error. See above.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 16 sentence: 'In seven of the 13 subgroups where G/P was	Amend to: 'In all of 13 subgroups	The ERG report is	Our wording regarding the subset

not cost effective, G/P was as effective as at least one cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).' This is inaccurate. In all of 13 subgroups where G/P was not cost effective, G/P was as effective as or more effective than at least one cost effective comparator. Furthermore, by definition, in all 13 of these subgroups G/P was not cost-effective because the ICER was above the cost effectiveness threshold, so the second sentence is redundant and misleading. This statement appears multiple times in the ERG report and should be amended each time (e.g. p. 113, p. 130, p. 133).	where G/P was not cost effective, G/P was as effective as or more effective than at least one cost effective comparator.'	inaccurate and misleading.	of 7 out of 13 subgroups where G/P was not cost effective was, in hindsight, not conveying the message that we wanted to convey. We have now altered the wording of that whole part of the text as follows: "For seven of the 13 subgroups where G/P was not considered cost effective, as it was dominated, G/P could be considered as approximately equivalent (same QALYs at only slightly higher costs, i.e. max £200) to the most cost-effective comparator, SOF/VEL. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was nearly equivalent to SOF/VEL, the most cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold)." We have made these alterations at all pages where we discussed these findings.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 16 sentence: 'The IFN eligibility was only considered for GT2, however it was not clear why there was no IFN	The ERG report should acknowledge the reasoning provided in the response	As explained, the ERG report does not	The company is correct, this statement was indeed incorrect

containing regimen as a comparator for the GT2 TN CC (IFN-eligible) subgroup.' This is inaccurate. No IFN-containing regimen was included as a comparator for the GT2 TN CC (IFN-eligible) subgroup because, as explained thoroughly in the response to the ERG clarification questions, peg-IFN + RBV is listed as a treatment option only for GT2 TN NC IFN-eligible patients in the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1). Therefore peg-IFN + RBV is not a relevant comparator for any subgroup except possibly GT2 TN NC IFN-eligible patients, so the submission did consider peg-IFN + RBV as a comparator for IFN-eligible GT2 TN CC patients.	to the ERG clarification questions here. Amend to: 'The IFN eligibility was only considered for GT2 TN NC, however, as there is no IFN containing regimen as a comparator for the GT2 TN CC subgroup.'	acknowledge explanations provided by the company in the response to the ERG clarification questions.	and we have changed the text in the report according to the company's suggestion.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 17 sentence: 'Furthermore, heterogeneity of the treatment-experienced population was not taken into account. (e.g. whether a patient is intolerant or an inadequate responder to the previous therapy, or has already received a DAA treatment or maybe is DAA naïve, may all impact the effectiveness of G/P).' It was not relevant to consider whether patients had previously received a DAA treatment because DAA-experienced patients do not fall within the licensed population for G/P.	The reference to previous DAA-treatment should be removed.	The ERG report criticises the company submission for not considering a factor that is specifically outwith the licensed indication of G/P.	Our statement regarding the subgroups that had not been taken into account was mostly in reference to the scope, which lists DAA experience as a factor. But we appreciate that the scope was written before the license was granted, and that given the current license most, if not all, DAA treatments would lead to ineligibility for treatment with G/P. We have therefore removed the reference to DAA-naive and DAA experienced patients.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 17: 'Similarly, the company assumed a zero-reinfection probability after reaching SVR and assumed that no natural recovery takes place, despite contrary evidence reported in the clinical literature.' Upon the request of the ERG, the company provided a scenario analysis assuming non-zero reinfection rates taken from the literature (response to ERG clarification question B4. This scenario analysis showed that the results were only slightly changed with no effect on the overall direction of the results. Therefore it is incorrect to say that the company did not take into account evidence reported in the clinical literature. This is repeated elsewhere in the ERG report (p. 130) and should be corrected there as well.	In citing this assumption made in the base case, the ERG report should acknowledge that in a scenario analysis provided by the company assuming non-zero reinfection rates in a subgroup, the results were only slightly changed with no effect on the overall direction of the results.	As described, the ERG report does not acknowledge the scenario analysis provided by the company.	On page 17 we have added: "However, scenario analysis by the company showed that the addition of these reinfection probabilities has only minimal impact on the results." Also in section 5.3 we now indicate for scenario 5 that the company already provided the scenario analysis for 1 subgroup, and that the ERG did the same for the other 25 subgroups.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 17-18: 'There are two major flaws in the probabilistic analyses presented by the company. The first is considering a single comparator instead of all possible comparators in the analyses. The second is the failure to include a large number of SVR and AE rates (i.e. all that have a value of 100% and 0%) in the probabilistic analyses. As a consequence, the ERG considers the PSA results in the CS unreliable. Given the time constraints and the model complexity, the ERG could not produce detailed (corrected) PSA results for all subgroups, only for a few example subgroups. If it is judged that the analysis of uncertainty is a major concern for this submission, the PSA analyses should	Change to: 'The ERG highlights two analytical choices made by the company in the probabilistic analysis: comparison to a single comparator and the decision not to vary SVR and AE rates with a value of 100% or 0%. Due to the complexity of the disease area and the vast number of subgroups,	As explained, these are not 'flaws' but pragmatic and reasoned approaches taken by the company for the PSA. Furthermore, due to the lack of context that list price analyses are not representative of the cost-effectiveness	No changes have been made. Regarding the first issue, comparing in the PSA against a single comparator, this may have been based upon pragmatic reasoning. However, even pragmatic choices need to be correct, which is not the case for the PSA. Maybe flaw is a bit strong, but the fact remains that the ERG considers this approach for the PSA wrong. At the time of the decision problem meeting, the ERG had no idea of the potential outcomes of the CE analyses, and was thus not in a position

be repeated after tackling the issues discussed in this report.' During the decision problem meeting between AbbVie, NICE and the ERG on the 6th of June 2017, the approach to sensitivity analyses was discussed, and all parties appeared content that a pragmatic approach to the health economic analysis is needed, owing to the complexity of the disease area and the vast number of subgroups. This was highlighted in the company's cover letter to the ERG's clarification questions. The discussion at the decision problem meeting included considering a single comparator instead of all possible comparators in the PSA and DSA and this was considered pragmatic. If the ERG subsequently decided that this approach was not appropriate, the ERG had the opportunity to ask the company to change this approach at clarification questions stage; however, this request was not made. Therefore, describing this as a 'flaw' is inaccurate – rather this was the pragmatic approach taken by the company following consultation with NICE and the ERG. Furthermore, the use of the Briggs correction is not without limitations, which is not acknowledged by the ERG. Arbitrarily inventing an additional patient who was assumed to fail treatment is not an evidence-based approach to PSA analyses; whilst it may be more justifiable in large sample sizes, it introduces large arbitrary negative effects in small subgroups, such as those in rare GTs. It may also be noted that the Briggs correction was neither applied to G/P nor to any other comparators, so the company's chosen methodology was balanced and did not favour any treatment over any other. The decision not to employ the Briggs correction was a considered and reasonable analytical approach taken by the company, not a 'flaw.' Finally, the alternative PSA analyses performed by the ERG	comparison to a single comparator is a pragmatic approach over comparison to all possible comparators, although the ERG has undertaken exploratory analyses in a small number of subgroups versus all comparators. The Briggs correction is one method that can be used to vary SVR and AE rates with a value of 100% or 0%, and the ERG has explored the effect of this alternative approach in a small number of subgroups. The ERG acknowledge that the Briggs approach has considerable limitations, particularly when implemented in small subgroups. However, it should be considered that these exploratory analyses were performed using the list price for all treatments, and therefore do not reflect the actual cost-effectiveness of G/P or comparator treatments to NHS England; when considered in the context of the confidential pricing analysis, these two analytic choices cease to be pertinent to the decision.'	of G/P and comparator treatments to NHS England due to discount price agreements, which renders list price analyses irrelevant to decision-making, the ERG report is misleading.	to foresee if for the PSA a comparison against 1 comparator would be possible or if the regular full comparison would be needed. Furthermore, where for the DSA only multiple pairwise comparisons are possible, yielding a number of tornado diagrams that would be totally impractical, for PSA the results remain within 1 graph per subgroup. Additionally, the company's model did already include a macro to generate a family of CEACs rather than 1 pairwise CEACs, so the company could have done the correct analysis with a minimal effort. Regarding the Briggs corrections, the ERG agrees that indeed this correction is not without limitations. However, this approach was already implemented by the company in the model, so simply checking this option was feasible for the ERG whilst making changes to the model to include a correct CI based on a Taylor-series approximations was not feasible in the time allowed. To illustrate the difference between the lower limits obtained by the Briggs approach versus the correct approach: If n=6, Briggs 0.577 correct 0.605 If n=10, Briggs 0.731 correct 0.741 If n=20 Briggs 0.86 correct 0.86 The fact that the company did not apply uncertainty in the PSA for all interventions, both G/P and the comparators is irrelevant in this context, as depending on the subgroup the intervention for which no uncertainty is assumed is different each time. So the impact of including uncertainty for all interventions differs per

– considering multiple comparators and using the Briggs methodology for varying SVR and AE rates which were 0% or 100% – are not relevant to decision-making because these analyses use list prices for G/P and comparators. As described in Issue 9, G/P and a number of comparators have agreed discounted prices, and therefore these list price analyses are not relevant to decision making. Therefore, this critique is not relevant to decision making. This should be acknowledged each time these 'flaws' are discussed (e.g. p.118–125, p. 131)			subgroup, but is certainly not negligible. Finally, the company argues that the alternative PSA analyses by the ERG are irrelevant for decision making, since they are based on list prices. This is true, but is equally true for all the results in the ERG report, including the results that are based on the company's model.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 19 sentence: 'Furthermore, all analyses were conducted on list prices, which may not reflect the actual costs of the treatments to the NHS.' As described in Issue 9, the ERG report does not acknowledge the pricing scenario analysis that was undertaken precisely to better reflect the actual cost of treatment to the NHS.	The ERG report should also report the results of the pricing scenario analysis, which are more relevant to decision making than the list price results.	As per Issue 9	No changes have been made. Including the pricing scenario of the company in the report would still not reflect the actual costs of the treatments to the NHS, as many of the comparators also have price arrangements through the CMU.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 20 sentence 'For example, there is no discussion in the CS of the proportion of people who fail to respond to current treatments or develop treatment resistance (specifically to DAA therapies).' The statement about the development of resistance to DAA	The reference to DAA therapies should be removed.	As explained, the statement is misleading and not relevant in the context of the licensed population for G/P treatment, which	Not a factual error.

therapies is misleading and not relevant in the context of the licensed population for G/P treatment, which excludes patients who have previously received DAA therapy.		excludes patients who have previously received DAA therapy.	

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 21 sentence 'The company claims that a number of NICE-approved therapies do not form part of clinical practice in England. This was based on expert clinical opinion and on a review of the European Association for the Study of the Liver (EASL) guidelines.' The key source of evidence used by the company to determine the comparators used in clinical practice was the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1). Furthermore, the wording 'the company claims' implies that the comparator choice is contentious. However, the comparator choice was well evidenced and the ERG comments that 'Our clinical expert supported that the three regimes highlighted in the bullet points above are no longer relevant to clinical practice,' indicating that the ERG should agree with the company's choice of comparators.	The June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1) should be added explaining clearly that these reflect the nationwide NHS England commissioning positioning, and the context that the ERG's own clinical experts supported the comparator choice should be added to the critique section. Amend to: 'The company submission noted that, as explained in the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1), NHS England stipulates the regimens used and therefore that a number of NICE-approved therapies mentioned in the final scope do not form part of clinical practice in England.'	The ERG report does not reflect the sources used in the company submission correctly and does not provide the context in the critique that the ERG's own clinical experts agreed with the company's choice of comparators.	Not a factual error. The list of comparators used by the company differed from the list of comparators issued by NICE in the final scope. Therefore, there is a degree of contention.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 30 sentence 'On 22 June 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Maviret, (glecaprevir/pibrentasvir) intended for the treatment of chronic hepatitis C in adults.[10]' This statement is out of date; at clarification stage the company informed NICE that the European Commission granted a marketing authorisation valid for G/P on 26 July 2017	Amend to 'On 26 July 2017 a marketing authorisation was granted for Maviret for the treatment of chronic hepatitis C virus (HCV) infection in adults'	Marketing authorisation has been granted;the ERG and NICE were informed of this prior to the development of the report.	Not a factual error. See above.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 31 sentence 'The company is negotiating a pricing agreement with the CMU.' This is factually inaccurate. The pricing agreement has been accepted, and this was explained on the ERG clarification call, the cover letter to the company's response to clarification questions, and in correspondence with the NICE.	The ERG report should acknowledge that this pricing agreement has been agreed. Amend to: 'A confidential pricing agreement with the CMU has been accepted.' The ERG report must further reflect this fact whenever list price analyses are mentioned to avoid inaccuracy by way of misleading omission.	The ERG report is factually incorrect.	Not a factual error. The description of the agreement is correct.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 38 sentence '… as only single arms from studies were included in the CS…. Observational data from included studies were used for comparative analyses between studies. These types of data are not suitable for comparative purposes. Therefore, the quality of all included studies is poor.' The statement "the quality of all included studies is poor" is inaccurate. This comment fails to acknowledge the context of the disease area, including the fact that there are multiple therapies that are considered essentially curative in this disease area. In light of this, there would be no clinical value in head-to-head comparative studies between treatments that are all equally expected to be curative. It would be unlikely that such studies could be powered to detect meaningful clinical differences between treatments, and it would be unethical to recruit patients to a study that did not have clinical usefulness. Regulatory bodies acknowledge this and have accepted non-controlled and single-armed studies for very highly efficacious treatments in this therapy area – not only for G/P, but for comparator products as well. The studies presented in the submission were accepted by the EMA as evidence to support granting of marketing authorisation for G/P. Given that regulatory bodies found the quality of the studies in the clinical trial programme for G/P acceptable in spite of the fact that the majority were not head-to-head studies, the ERG's criticism that all the included studies are poor is exaggerated.	This statement should be amended to "However, within the specific context of comparing curative therapies for an otherwise incurable infection, the quality of all included studies is acceptable."	The ERG comment does not consider the wider context of the disease area and the curative nature of the therapies involved. and the ERG is therefore overly critical and their opinion is at odds with that of regulatory bodies and clinicians, who find the evidence presented acceptable when taken within the broader disease context. For further discussion on this topic see: "Draft Guideline on the clinical evaluation of direct acting antivirals for the treatment of chronic hepatitis" available on the EMA website, which states: *"However, spontaneous resolution of chronic HCV infection in the absence of therapy is a very rare event. Therefore, studies without an active, prospective randomised control constituting an approved and*	Not a factual error. The quality of the evidence is poor for the purpose for which it used, i.e. a comparative analysis.

		recommended regimen may be sufficiently informative if SVR12 rates are anticipated to be very high (e.g., around 95%).”	

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 49 value for ENDURANCE-3 (G/P 8 weeks), number of and % of patients with GT3 infection is described 115 (100); this is incorrect.	The number and % of ENDURANCE-3 patients enrolled to receive G/P for 8 weeks should be changed to the correct value, 157 (100).	The ERG report is incorrect.	This has been corrected.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 55 statements: ‘From these subgroups, the company provided results for people co-infected with HIV (ENDURANCE-1 - GT1/NC/TN+TE). No results are provided for any of the other subgroups that were used in the economic model.’ These statements are incorrect. Regarding the first sentence, the company submission did not provide results for the subset of patients with HIV co-infection from ENDURANCE-1, which this sentence from the ERG report implies. The patient population in EXPEDITION-2 had HIV co-infection, and the company submission reported results for people co-infected with HIV from EXPEDITION-2. Clinical efficacy results for some patient subgroups in the bulleted list on p. 54 – 55 were provided, for example patients	This first sentence should be amended as follows: ‘From these subgroups, the company provided results for people co-infected with HIV (EXPEDITION-2), patients with and without renal impairment (EXPEDIGION-4) and patients who had previously received DAA containing-regimens (MAGELLAN-I). It should be noted that the patient population in MAGELLAN-I is not in line with the license for G/P.’ The second sentence should be removed.	The ERG report omits results presented in the company submission.	The reference to (ENDURANCE-1 - GT1/NC/TN+TE) is corrected to (EXPEDITION-2). The other studies were not used in the economic model (see ERG report Table 4.2).

with and without renal impairment (subgroup results for EXPEDITION-4) and patients who had previously received DAA containing-regimens (MAGELLAN-I population). The sentence in the ERG report contradicts this. It should be noted that the patient population in MAGELLAN-I is not in line with the license for G/P. Regarding the second sentence, results are provided for all subgroups used in the economic model in section B.2.7.1 on p. 108 of the submission.			

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 56 insomnia AE rate values for ENDURANCE-3 treatment arms are described as 'NR.' This is incorrect.	[redacted]	The ERG report is incorrect.	This has been added.

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 56 upper respiratory infection AE rate values for ENDURANCE-3 treatment arms are not marked as academic in confidence, as in the company submission.	[redacted]	These values were taken from the study CSR when presented in the company submission, and have not been published.	AiC marking has been added.

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 59 Table 4.13, no data are marked as confidential. All of the data (named adverse events and frequencies) were extracted from the CSR and have not been published.	The named adverse events and all frequencies should be marked as academic in confidence.	The information reported in this table has not been published.	AiC marking has been added.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 75 statement 'Results of comparator interventions are only reported as inputs for the economic model (Section B3.3 Clinical parameters and variables)' is inaccurate. SVR12 rates reported by the studies identified by the SLR for comparator therapies are described in Table 130 of the appendix, as prescribed by the STA template.	The ERG report should acknowledge that results of comparator interventions were also reported in the Appendix, which is the correct location prescribed by the recently updated NICE STA template, and not just as inputs in the economic model.	The ERG report omits results presented in the company submission.	Not a factual error, we were referring to the main CS.

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 75 statement 'The company acknowledges that this is associated with limitations, but does not describe any of these limitations. In fact, the section in the CS describing the uncertainties in the indirect and mixed treatment comparisons consists of two words: "Not applicable". The company did not complete B.2.10.0 (Uncertainties in the indirect and mixed treatment comparisons) because no indirect or mixed treatment comparisons were performed, and	Please remove the sentence beginning 'in fact.'	As described, the company followed the STA template, and following the template accurately should not be grounds for criticism by the ERG.	Not a factual error.

therefore it was not necessary to complete this section. The company followed the STA template, and following the template accurately should not be grounds for criticism by the ERG.			

Issue 29

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 75 statement 'The company selected one source for each intervention and population.' This is incorrect. For interventions where multiple Phase II or III trials or arms of the trials were available, data were pooled from these trials e.g. • GT1 TN NC OBV/PTV/RTV + DSV ± RBV – PEARL-IV and SAPPHIRE-I • GT2 TN NC SOF + RBV – FISSION, VALENCE and ASTRAL-2 • GT2 TE NC SOF + RBV – FUSION, VALENCE and ASTRAL-3 • GT3 TN CC and GT3 TE CC SOF/VEL – ASTRAL-3 and POLARIS-3 • GT3 TN NC SOF + DCV ± RBV – ENDURANCE-3 and ALLY-3 • GT3 TN CC SOF + RBV – VALENCE and ASTRAL-3	This sentence could be reworded as: 'The company selected one source for each intervention and population, though in cases where multiple Phase II/III trials or arms of the trials were available for an intervention in a specific population these data were pooled.'	For interventions where multiple Phase III trials were available, data were pooled from these trials as described. The ERG report omits this.	Not a factual error, see response to issue 7.

Issue 30

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 75 sentence 'Although the ERG agrees that it is not feasible to form any network between G/P and any relevant comparator therapies and that the limited availability of	The ERG report should acknowledge the accepted historical precedent for	As explained, the ERG report does not	Not a factual error. Even if it is the only possible

baseline characteristics for comparator studies precludes an adjusted analysis, it should be taken into account that the results of these naïve indirect comparisons are unreliable.' The ERG describes the methodology used by the company as unreliable, but does not present or even suggest an alternative approach. On p. 38 the ERG report reads 'The ERG agrees that a meta-analysis of G/P studies is not feasible.' If no alternative approach is possible and the ERG agrees that a meta-analysis is not feasible, it should be acknowledged that though this method may be associated with uncertainty, there is an accepted historical precedent for this method in previous NICE appraisals, and without any suitable alternatives it is therefore the only possible method.	this methodology and that without any suitable alternatives this is the best possible method given the nature of evidence base.	acknowledge that the accepted historical precedent for this methodology and the lack of suitable alternative methods.	method, it can still be unreliable.

Issue 31

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
P. 76 sentence: 'If the results of a poorly performed adjusted simulated treatment comparison based on single arm studies (unanchored) are 'not worthy of consideration', surely the results of a naïve comparison without any attempt at adjustment are even less worthy of consideration.' The ERG do not provide any evidence or analysis to justify their assertion with respect to the data presented. Furthermore, for the ERG to selectively quote from a single published paper which critiqued an entirely different data analysis and imply that this critique is transferable to the present appraisal is unscientific; words such as "surely" ought not to be present in any ERG report. It may be noted that the ERG do not provide any suggested alternative analytical framework, nor do they strongly acknowledge that this issue is present in previous NICE appraisals of DAAs that resulted in positive recommendations.	The ERG do not provide evidence or analysis to back their assertion and therefore this section of the report should be removed.	This statement is not based on evidence or analysis.	Not a factual error.

Issue 32

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 77 statement: 'The CSR shows that a SVR12 rate of [redacted] was achieved in HCV GT3-infected patients with compensated cirrhosis or without cirrhosis and with or without prior pegylated IFN/ribavirin experience who were treated with 12 weeks of G/P.[64] [redacted].	These sentences should be marked as academic in confidence.	The information reported in these sentences was taken from the study CSR has not been published.	AiC marking has been added.

Issue 33

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 106 statement: 'Note that the company has opted not to model the AE-related disutility explicitly, but instead has chosen to apply a treatment-related change in utility for all treatments for the duration of the treatment. Hence, the exact selection of AEs to include in the model can only impact the cost outcome, not the QALY outcome.' While it is true that the AEs with costs in the model impacted the cost outcome, this sentence implies that AEs did not impact the QALY outcome *at all*. The treatment-related change in health utility captures all the effects of treatment on patient QoL, including all treatment-related AEs, and therefore in this way all possible AEs impacts QALY. This is why utility decrements for individual AEs were not also applied, as this may lead to double-counting of the effect of AEs on QoL.	The statement in the ERG report should acknowledge that although only those AEs with costs in the model affect total costs, all possible treatment-related AEs affected QALYs due to the incorporation of treatment-related change in health utility.	The statement in the ERG report is misleading and implies that AEs did not affect QALYs at all in the model.	No changes have been made. In the text from the ERG report quoted by the company it is clear that we refer to 'the exact selection of AEs to include in the model' as not impacting QALYs. This does not say or imply that AEs in general do not impact QALY of patients.

Issue 34

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 108, the G/P entries in Table 5.12. These are incorrect – two values are displayed for each G/P entry, when only one value (the one on the left) is the correct annualised input in the model. The values on the right-hand side appear to be the raw values that were subsequently annualised; however, it is incorrect to report them in a column titled 'Annualised change in treatment-related health utility.'	G/P (8) [redacted] G/P (12) [redacted] G/P (16) [redacted]	The original ERG report erroneously has two inputs in the 'annualised change in treatment-related health utility' column.	This is not a factual error from the ERG but from the company. The ERG report has two inputs erroneously in the annualised change column for the mere reason that the company had these two inputs erroneously in the annualised change column.

Issue 35

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 109 statement: 'In Section 5.3 the results of the scenario analysis as run by the ERG are presented' it should be noted that in Section 5.3 the ERG concludes that the change made in this scenario analysis had 'no impact on the ranking of G/P regarding cost effectiveness and total costs.'	The ERG report should add this conclusion in Section 5.2.8.	In the previous paragraph in 5.2.8, the fact that a different scenario (SVR gain of 0) had only a minimal impact on the results was described. When describing the scenario in question (no treatment-related health utility adjustment), the ERG report does not explain the results of the scenario analysis at all in Section 5.2.8, implying that in contrast to the previous scenario, this scenario did have a significant effect on the results. However, the	This is not a factual error. In the first case (SVR gain of 0) the summarizing table (not shown) is exactly the same as table 5.17 for the base case. For the second scenario (no treatment-related health utility adjustment) the summarizing table, 5.23, is not exactly the same as 5.17. This explains the reason why the ERG opted to keep the reference in 5.2.8 to 5.3 purely as a reference, without already including the conclusion. We have opted to remove the text ", showing only a minimal impact on the results." where it refers to the 'SVR gain of 0' scenario, to

		conclusion in Section 5.3 is that the scenario had no impact. Therefore the wording in the ERG report is misleading.	achieve consistency between both scenario analyses.

Issue 36

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 113 statement: 'Given the high level of uncertainty associated with the input parameters of the model…' This is a sweeping statement that implies that all inputs in the model are subject to high uncertainty. The sections above discuss the company's approach to model inputs, and although it is acknowledged that there are limitations to using naïve indirect comparisons for treatment-related inputs, this is not the case for other health and cost-related inputs. The uncertainty of these inputs is not quantified, so it is not justifiable to describe all inputs as highly uncertain without quantification. This statement is repeated on p. 118 and should be amended there as well.	Change to: 'Therefore there is uncertainty around some model inputs.'	As described, this is a sweeping statement and there is no quantification of the level of uncertainty of all model inputs to support it.	We have altered the quoted sentence to indicate clearly that there is high uncertainty for some of the efficacy input parameters due to very small sample sizes.

Issue 37

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 117 statement 'The ERG considers that choosing a single comparator is methodologically incorrect and the interpretation of results can be potentially misleading' in the context of presenting sensitivity analyses against a single comparator	Amend to: 'The ERG considers that choosing a single comparator is methodologically incorrect for PSA (though not for DSA)	As described, this statement currently contradicts the ERG's comment later in the report	We have added the words 'in a PSA' to the quoted sentence.

treatment. This statement is at odds with the ERG comment on the DSA analysis on p. 124: 'Results were provided for G/P compared to a single comparator in each subgroup. Unlike PSAs, the ERG considers that this can be considered a pragmatic approach to DSA since an alternative methodology involving all comparators seems difficult to perform in practice.' The ERG ought to clarify that this sentence applies only to their view on PSA not DSA	and the interpretation of PSA results can be potentially misleading'	with respect to DSA. The amendment will correct this point.	

Issue 38

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 127 statement: 'this section, the ERG conducted additional scenario analyses on the company base-case to explore the uncertainty around the assumptions taken in the company's base-case analysis. The ERG refrained from setting a preferred base-case, due to the concerns about the uncertainty surrounding SVR rates for the intervention and its comparators, which are caused by small sample sizes for some groups (e.g. n=2) as well as the method used to compare the effectiveness between treatments (naïve indirect comparison). Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses' In the report's statement 'The ERG refrained from setting a preferred base-case due to concerns…' it should be noted that elsewhere the ERG, e.g. p. 17: 'Despite the several uncertainties present in the CS base-case, the ERG did not produce an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisal.' This section on p. 127 reads as overly critical of the company's base case because the context that the ERG itself could not	The context that the ERG did not produce an alternative base-case because it was not clear that any alternative base-case assumptions would be properly justified should be added here to avoid misrepresentation by omission.	As described, this section appears overly critical without the context that no alternative base cases were considered justifiable by the ERG; as it stands it is not an accurate representation of the ERG conclusions.	Upon rereading our text we realize we focussed e.g. on page 17 on the point estimates, and for those we did not consider an alternative base-case necessary. However, the issue regarding the non-inclusion of uncertainty whenever a rate is 100% or 0% is serious, and was addressed in section 5.2.11, rather than 5.3. Our quoted sentence on page 127 suggests that it is *due* to the uncertainty that we did not set out own preferred base-case, this should have read *despite* the uncertainty. We have altered the text accordingly. Also on page 17 for example, we have added 'assumptions regarding point estimates and

identify any alternative base-case assumptions that would be properly justified is omitted. Furthermore, in the introduction section to the scenarios it should be stated up front that none of the scenarios had an impact on the base-case results, in line with the fact that the assumptions made by the company in the base case were properly justified.			structure'.

Issue 39

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 129 sentence: 'While the economic model is in line with the decision problem formulated by the company, it is only partially in line with the scope…other relevant comparators listed in the NICE scope [1) DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE); 2) IFN with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients); 3) SOF in combination with RBV, with or without IFN (for specific people with GT1 and GT4; as recommended by NICE)] were not included in the company's cost effectiveness analysis because, according to the company, these are not used in current NHS practice.' On p. 22 the ERG report comments that 'Our clinical expert supported that the three regimes highlighted in the bullet points above are no longer relevant to clinical practice,' indicating that the ERG should agree with the company's choice of comparators. Therefore this is not an accurate criticism of the deviation from the scope, as it is supported by evidence provided by the company and evidence gathered by the ERG.	Remove comparator choice as an example of unjustified deviation from the scope.	As described, the ERG heard from their own clinical experts that the comparator choice made by the company, which deviated from the scope, accurately reflected clinical practice.	In this paragraph the ERG does not make any claim whether or not the deviations from the scope could be considered unjustified, these deviations are just observed. However, upon rereading we realise that the wording of 'other relevant comparators' in this context is unfortunate, so we have removed the word 'relevant'.

Issue 40

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 134 statement: 'Two scenario analyses conducted by the company first demonstrated how the cost effectiveness of G/P might change after the CMU price agreement (when comparators from other companies were based on list prices).' As described in previous issues, the results of this analysis – which are not mentioned in the report - should be the focus of the report as these are the most relevant to decision-making as they more accurately reflect the cost-effectiveness of G/P to NHS England versus the list price analyses.	As per previous issues on this subject.	As per previous issues on this subject.	No changes have been made. Including the pricing scenario of the company in the ERG report would still not reflect the actual costs of the treatments to the NHS, as many of the comparators also have price arrangements through the CMU. As such, this scenario does not reflect the cost-effectiveness of G/P more accurately. It should also be noted that the outcomes of this pricing scenario are still available to the committee through the company submission.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Glecaprevir-pibrentasvir 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:**
14	AiC marking has been added
15	We corrected the statement that four instead of three of the 24 subgroups included more than 100 patients.
16	"For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator." was replaced by "For seven of the 13 subgroups where G/P was not considered cost effective, as it was dominated, G/P could be considered as approximately equivalent (same QALYs at only slightly higher costs, i.e. max £200) to the most cost-effective comparator, SOL/VEL. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was nearly equivalent to SOL/VEL, the most cost effective comparator." AND: "The IFN eligibility was only considered for GT2, however it was not clear why there was no IFN containing regimen as a comparator for the GT2 TN CC (IFN-eligible) subgroup." was replaced by: "The IFN eligibility was only considered for GT2 TN NC, however, as there is no IFN containing regimen as a comparator for the GT2 TN CC subgroup."
17	"(e.g. whether a patient is intolerant or an inadequate responder to the previous therapy, or has already received a DAA treatment or maybe is DAA naïve, may all impact the effectiveness of G/P)." was replaced by "(e.g. whether a patient is intolerant or an inadequate responder to the previous therapy may impact the effectiveness of G/P)." We added: "However, scenario analysis by the company showed that the addition of these reinfection probabilities has only minimal impact on the results." and "since it was not clear that any alternative base-case assumptions would be properly justified, "

	was replaced by "since it was not clear that any alternative base-case assumptions regarding point estimates and structure would be properly justified, "
18	We corrected the statement that four instead of three of the 24 subgroups included more than 100 patients.
19	"since it was not clear that any alternative base-case assumptions would be properly justified," was replaced by "since it was not clear that any alternative base-case assumptions regarding point estimates and structure would be properly justified,"
48	The number and % of ENDURANCE-3 patients has been corrected
53	AiC marking has been added We corrected the statement that four instead of three of the 24 subgroups included more than 100 patients.
54	The reference to (ENDURANCE-1 - GT1/NC/TN+TE) is corrected to (EXPEDITION-2).
55	Insomnia rates have been added and AiC marking has been added
58	AiC marking has been added
76	We corrected the statement that four instead of three of the 24 subgroups included more than 100 patients. AiC marking has been added
88	Text added: "In response to the clarification letter, the company performed a scenario analysis showing for one subgroup that the addition of these reinfection probabilities had only minimal impact on the results."
92	We corrected the statement that four instead of three of the 24 subgroups included more than 100 patients.
108	Text added: ", showing only a small impact on the results.
112	"Given the high level of uncertainty associated with the input parameters of the model, the ERG chose to describe the cost effectiveness results in this section based on the £20,000 threshold." was replaced by "Given the high level of uncertainty associated with some of the efficacy input parameters of the model (due the small sample sizes on which they are based), the ERG chose to describe the cost effectiveness results in this section based on the £20,000 threshold." and "For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. This is indicated with shaded cells in Table 5.17. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups

	where G/P was not cost effective, G/P was as effective as at least one cost effective comparator." was replaced by "For seven of the 13 subgroups where G/P was not considered cost effective as it was dominated, G/P could be considered as approximately equivalent (same QALYs at only slightly higher costs, i.e. max £200) to the most cost-effective comparator, SOL/VEL. This is indicated with shaded cells in Table 5.17. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was nearly equivalent to SOL/VEL, the most cost effective comparator. "
116	"in a PSA" added
126	'due to' replaced by 'despite' Text added: "The impact of including uncertainty appropriately for 100% SVR rates and 0% AE rates was already addressed in section 5.2.11."
127	Text added: "This scenario was performed by the company in response to the clarification letter for one subgroup, and was repeated by the ERG for all subgroups."
128	Text removed: 'relevant'
129	Text added: "However, a scenario analysis by the company showed that the addition of these reinfection probabilities has only minimal impact on the results." "For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator." replaced by "For seven of the 13 subgroups where G/P was not considered cost effective, as it was dominated, G/P could be considered as approximately equivalent (same QALYs at only slightly higher costs, i.e. max £200) to the most cost-effective comparator, SOL/VEL. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was nearly equivalent to SOL/VEL, the most cost effective comparator. "
132	AiC marking has been added AND: "For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although

	G/P was dominated, it can be considered as equally effective as these comparators. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator." replaced by "For seven of the 13 subgroups where G/P was not considered cost effective, as it was dominated, G/P could be considered as approximately equivalent (same QALYs at only slightly higher costs, i.e. max £200) to the most cost-effective comparator, SOL/VEL. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was nearly equivalent to SOL/VEL, the most cost effective comparator."
133	We corrected the statement that four instead of three of the 24 subgroups included more than 100 patients. AND: text added: regarding point estimates and structure

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 glecaprevir-pibrentasvir (G/P) 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, daclatasvir (DCV) in combination with sofosbuvir (SOF) (for GT1 and GT4); pegylated-interferon alfa (IFN) with RBV and SOF in combination with RBV (for GT1 and GT4) were not included in the decision problem. The rationale for these omissions, as supplied by the company, states that these treatment regimens are not used in current NHS practice.

The company's model does not include the development of resistance to G/P and other comparators based on the assumption that this outcome does not impact the cost effectiveness of G/P. Also, separate subgroup analyses for patients who are co-infected with HIV, previous treatment received (with or without DAA-containing regimens), people who have received treatment before liver transplantation, and those who have received it after liver transplantation, response to previous treatment (non-response, partial response, relapsed), and people with and without renal impairment were not presented, as it was deemed infeasible by the company.

1.2 Summary of clinical effectiveness evidence submitted by the company

Eighty-one publications (reporting on 79 studies) were identified as meeting the eligibility criteria. Fourteen of these publications, representing seven studies, involved G/P. In addition, information on four further clinical studies of G/P in patients with CHC are mentioned in the company submission. These studies were conducted in special populations of patients with HIV co-infection, renal impairment, failure on prior DAAs and a post-transplant population. Finally, the company mentioned two trials in Japanese patients with CHC: CERTAIN-1 and CERTAIN-2. These trials are only minimally discussed in the CS and not included in the economic model. According to the company, this exclusion was because "these two trials were conducted entirely in Japanese patients" which "precludes their generalisability to the UK patient population and subsequently their use in the economic model". Apart from these two trials in Japanese patients, none of the included studies presented comparative data for the licensed treatment duration of G/P with any of the comparators.

The G/P studies included patients with all genotypes; treatment-naïve and treatment-experienced patient populations; and patients with 'no cirrhosis or compensated cirrhosis'.

When split by cirrhosis status and previous treatment (naïve or experienced), SVR rates were consistently above 90% for all genotypes, except for GT2/TE/NC ([redacted] in SURVEYOR-II, Part 4; but [redacted] in SURVEYOR-II, Parts 1 and 2), GT3/TE/CC ([redacted] in SURVEYOR-II, Part 2; but [redacted] in SURVEYOR-II, Part 3) and GT6/TN/NC ([redacted] in SURVEYOR-II, Part 4).

[redacted]. In studies without a comparator, many treatment arms [redacted]

According to the company, G/P had a favourable safety profile that was similar to placebo and SOF/DCV, and that was similar across treatment durations of 8, 12, and 16 weeks. G/P was well tolerated across a broad and diverse population of patients, including patients with CC, HIV co-

infection, and CKD Stage 4/5. Common study adverse drug reactions (ADRs) occurring in ≥5% of patients were headache, fatigue, and nausea. Adverse drug reactions were mostly Grade 1 (mild) in severity. Serious ADRs and ADRs leading to premature study drug discontinuation were rare (≤0.1%).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company submission (CS) and response to clarification provided sufficient detail for the ERG to appraise the searches for eligible trials. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4 using a good range of databases. Additional searches of conference proceedings were conducted but no separate literature searches were undertaken to identify adverse events data, non-randomised and non-controlled evidence.

The conclusion from the G/P studies is that G/P has high SVR rates in all genotypes. In addition, G/P has a relative favourable safety and tolerability profile. However, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each group. Only four out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC, GT2/TN/NC and GT3/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators relies on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. In most cases the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.

1.4 Summary of cost effectiveness submitted evidence by the company

The company developed a de novo cost effectiveness model to assess the cost effectiveness of G/P compared to nine different comparators: BSC-watchful waiting, DCV/SOF, DCV/SOF/RBV, EBR/GZR, LDV/SOF, OBV/PTV/DSV+DSV ± RBV, PR, SOF/PR, SOF/RBV and SOF/VEL. The cost effectiveness analyses performed by the company are in line with previous STAs for HCV treatments. The population considered in the cost effectiveness analyses was sub-divided into 26 different subgroups, where patients were stratified by genotypes (GT1, GT2, GT3, GT4, GT5 and GT6), treatment experience (treatment-naïve and treatment-experienced patients), cirrhosis status (cirrhotic and non-cirrhotic patients) and IFN-eligibility (only for GT2 TN patients). Full incremental cost effectiveness results were presented for all subgroups. A National Health Service (NHS) and Personal and Social Services (PSS) perspective was adopted with a lifetime time horizon. A 3.5% discount rate was used for both costs and quality-adjusted life years (QALYs).

The cost effectiveness model developed for this submission was a Markov model which consists of 13 health states. Non-cirrhotic patients start from states F0-F3, and cirrhotic patients start from F4. All treatment related outcomes (achieving SVR, treatment related adverse events and discontinuation) occur within the first year of the model. Patients who do not achieve SVR are at risk of progressing to more severe states. Patients who reach F4 can progress to DC and HCC states, which may lead to liver transplantation and liver-related death. The liver transplantation state was divided into two categories (first year and later years).

Treatment effectiveness was modelled as the probability of achieving SVR. Other treatment-specific parameters included adverse event rates, treatment duration, and treatment-related utility adjustments.

All these parameter estimates were based on naïve indirect comparison of clinical trials assessing the efficacy of G/P and its comparators in the relevant subgroups.

The model uses health state based utilities from the literature (utilities that were used in Wright et al. 2006 and Ratcliffe et al. 2002) in line with previous STAs for HCV treatments. A utility increment due to SVR is applied based on Shepherd et al. 2007 and Hartwell et al. 2011. Treatment-related health utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events.

List prices were used as treatment costs for G/P and the comparator treatments in the cost effectiveness analysis. Health state costs (disease management costs based on disease stage) and other costs for adverse events were based on literature, expert opinion, UK reference costs and previous appraisals for HCV (especially TA430).

The base-case cost effectiveness results showed that for non-cirrhotic patients, G/P was always cost effective except for two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For seven of the 13 subgroups where G/P was not considered cost effective, as it was dominated, G/P could be considered as approximately equivalent (same QALYs at only slightly higher costs, i.e. max £200) to the most cost-effective comparator, SOF/VEL. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was nearly equivalent to SOF/VEL, the most cost-effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).

Additionally, the company conducted probabilistic, deterministic and scenario analyses. Probabilistic results were reported as the probability that G/P is cost effective against one single comparator for each subgroup at £20,000 and £30,000 thresholds. The comparator was selected as the one against which G/P had the lowest incremental net monetary benefit when valuing a QALY at £20,000. The result of the deterministic sensitivity analyses showed that in general the ICER was most sensitive to changes in SVR rates. Two scenario analyses conducted by the company first demonstrated how the cost effectiveness of G/P might change after the CMU price agreement (when comparators from other companies were based on list prices). Second, it was shown that using trial-based utilities increased total QALY estimates compared to the base-case when literature-based utilities were used as input.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The CS and response to clarification provided sufficient detail for the ERG to appraise the cost effectiveness searches. Searches were well documented but not all searches were reproducible in line with the NICE guide to the methods of technology appraisal. However, a good range of databases were searched and additional searches of conference proceedings were also undertaken.

The following treatments were not included in the cost effectiveness analyses because, according to the company, these are not used in current NHS practice: 1) DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE); 2) IFN with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients); 3) SOF in combination with RBV, with or without IFN (for specific people with GT1 and GT4; as recommended by NICE). The IFN eligibility was only considered for GT2 TN NC, however, as there is no IFN containing regimen as a comparator for the GT2 TN CC subgroup.

Despite being included in the final scope, the company did not perform subgroup analyses for patients who are co-infected with HIV and post-liver transplantation. The subgroup of patients who are intolerant to or ineligible for interferon treatment were only considered for GT2 TN patients. Since these excluded groups (e.g. HIV co-infected patients) were also not taken into consideration while deriving some of the model input estimates (e.g. utility), transferability of the current results for these groups is disputable. Furthermore, heterogeneity of the treatment-experienced population was not taken into account. (e.g. whether a patient is intolerant or an inadequate responder to the previous therapy may impact the effectiveness of G/P).

Onward transmission is not included in the economic model. Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework. Similarly, the company assumed a zero-reinfection probability after reaching SVR and assumed that no natural recovery takes place, despite contrary evidence reported in the clinical literature. However, scenario analysis by the company showed that the addition of these reinfection probabilities has only minimal impact on the results.

SVR rates, adverse event rates, treatment duration, and treatment-related utility adjustments were based on naïve indirect comparisons of clinical trials assessing the efficacy of G/P and its comparators in the relevant subgroups. The ERG has concerns on the plausibility of this approach, which is not in line with evidence synthesis best practices and is susceptible to bias. Furthermore, some of the SVR rates were either derived from very small sample sizes or the effectiveness in a subgroup was assumed to hold in another subgroup. Since SVR rates are the main driver of costs and effectiveness, all these assumptions create a substantial uncertainty on the cost effectiveness of G/P.

Furthermore, it was not clear to the ERG why age-dependent transition probabilities were not updated every year.

The health state utilities from RCTs could have been used by the company in their cost effectiveness analysis instead of the utilities from the literature. The ERG questions to what extent utility values published in 2006 (originating from EQ-5D questionnaires completed in 2002), i.e. before the DAA-era, can be seen as representative of UK patients currently suffering with CHC. Similarly, the RCT-based utility values show a difference in utility with or without SVR ranging from 0.025 to 0.029, substantially lower than the increment of 0.05 applied by the company based on Wright et al. 2016 thus raising doubt about the validity of the latter value.

The ERG was unsure about the completeness of the health state cost estimates used in the model, as items such as GP visits and home care costs are not included.

The ERG is concerned over the validation status of the cost effectiveness analysis by the company. The tests conducted for the technical verification of the model were not presented and the only validation effort was the external validation of the model estimates of the cirrhosis risk in 20 years from the clinical literature.

Despite the several uncertainties present in the CS base-case, the ERG did not produce an alternative base-case, since it was not clear that any alternative base-case assumptions regarding point estimates and structure would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses.

failure to include a large number of SVR and AE rates (i.e. all that have a value of 100% and 0%) in the probabilistic analyses. As a consequence, the ERG considers the PSA results in the CS unreliable. Given the time constraints and the model complexity, the ERG could not produce detailed (corrected) PSA results for all subgroups, only for a few example subgroups. If it is judged that the analysis of uncertainty is a major concern for this submission, the PSA analyses should be repeated after tackling the issues discussed in this report.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The majority of searches for eligible studies in the CS were well documented. Searches were carried out in a good range of databases and strategies utilised study design filters. In response to clarification questions, a number of searches were repeated to ensure all relevant evidence had been included. Supplementary searches of conference proceedings were also undertaken.

The company's submitted evidence on clinical effectiveness broadly covered the final scope set out by NICE. The review of G/P studies included all relevant studies in which G/P 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 structure of the economic model developed by the company is in line with previous models presented in appraisals for HCV submitted to NICE. Thus, the model structure (not necessarily inputs) reflects the main aspects of the chronic HCV disease. The model also includes relevant adverse events, utilities and costs.

1.6.2 Weaknesses and areas of uncertainty

Clinical effectiveness searches were re-run in response to clarification questions but did not include a number of comparators from the original search. Conference searches also did not look for the intervention of interest in addition to some comparator interventions. Cost effectiveness searches that were re-run in response to clarification questions added a restrictive UK country filter, which may have resulted in relevant evidence being missed. There is also concern about the effectiveness of the Embase search for health-related quality of life as the company did not present the full set of records that they claimed to have screened. Some searches were also not reproducible in line with NICE guide to the methods of technology appraisal. There were no searches for adverse events data, non-randomised and non-controlled evidence.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators rely on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how responses and adverse events for comparator studies were selected and whether all possible sources were used. In most cases, the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.

In addition, patient numbers for most GT4, GT5 and GT6 populations in G/P studies are very low, often less than 10 patients in each subgroup. Only four out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC, GT2/TN/NC and GT3/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

Since the key parameters in the cost effectiveness analyses (SVR rates) were based on the treatment effectiveness data, all health economic analyses suffer from the uncertainty of clinical effectiveness (i.e. comparative SVR rates). Furthermore, all analyses were conducted on list prices, which may not reflect the actual costs of the treatments to the NHS. Both probabilistic and sensitivity analyses presented by the company were performed incorrectly. As a consequence, the ERG considers the sensitivity analysis results in the CS unreliable. If it is judged that the analysis of uncertainty is a major concern for this submission, these analyses should be repeated after tackling the issues discussed in this report. The company submission would also benefit from a more transparent electronic model.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has not presented an alternative base-case, since it was not clear that any alternative base-case assumptions regarding point estimates and structure would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses. In the scenario analyses assumptions surrounding the utility gain due to SVR, impact of the treatment on utility, impact of age on utility were challenged. In addition, alternative inputs for transition probabilities between fibrosis stages and re-infection rates were explored. Even though these scenarios changed the total costs and/or total QALYs estimates, the impact on incremental results was minimal. The cost effectiveness of G/P in each subgroup did not change, hence the cost effectiveness results of the base-case seem to be robust to changes in utility and treatment-unrelated clinical model inputs.

Additionally, the exploratory PSA analyses conducted by the ERG showed that that the inclusion of parameter uncertainty around all SVR and AE rates (which was not included in the company's base-case when rates were 100% or 0%) can have a major impact on the G/P cost effectiveness probability for certain subgroups; but also that this impact can go in either direction (although more frequently it decreases the G/P cost effectiveness probability). This was especially striking for GT5 TN NC patients, for whom the company might have overestimated the probability of G/P being cost effectiveness by 66 percent. Furthermore, the ERG showed that the PSA outcomes were enormously scattered over the CE plane quadrants for a number of subgroups, which illustrates the main limitation of presenting cost effectiveness probabilities alone (as in the CS).

Table Error! No text of specified style in document.**.1: Baseline characteristics for relevant G/P studies (ENDURANCE and EXPEDITION) - continued**

	ENDURANCE-1[18, 39]	**ENDURANCE-3**[20, 43]	**EXPEDITION-1**[47]
Baseline characteristics, n (%)	G/P 8 weeks (N=351)	G/P 8 weeks (N=157)	G/P 12 weeks (N=146)
HCV genotype			
1 (total)	[redacted]	-	87 (59.6)
1a	152 (43.3)	-	[redacted]
1b	[redacted]	-	[redacted]
2 (total)	-	-	34 (23.3)
3 (total)	-	157 (100)	-
4 (total)	-	-	16 (11.0)
5 (total)	-	-	2 (1.4)
6 (total)	-	-	7 (4.8)

Source: CS, Tables 16, 17, 20 and 21, pages 75-89.
CC = compensated cirrhosis; DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; SOF = sofosbuvir; HCV = hepatitis C virus; NC = non-cirrhotic; RBV = ribavirin

Genotype	Subgroup	Study	Regimen	SVR12
		SURVEYOR-II, Part 3[24, 52]	G/P 16 weeks:	[redacted]
GT4–6	TN NC	GT4: SURVEYOR-II, Part 4[52]	G/P 8 weeks	[redacted]
		GT5: SURVEYOR-II, Part 4[52]	G/P 8 weeks	[redacted]
		GT6: SURVEYOR-II, Part 4[52]	G/P 8 weeks	[redacted]
	TN CC	GT4: EXPEDITION-1[47]	G/P 12 weeks	[redacted]
		GT5: EXPEDITION-1[47]	G/P 12 weeks	[redacted]
		GT6: EXPEDITION-1[47]	G/P 12 weeks	[redacted]
	TE NC	GT4–6: SURVEYOR-II, Part 4[52]	G/P 8 weeks	[redacted]
	TE CC	GT4–6: EXPEDITION-1[47]	G/P 12 weeks	[redacted]
Source: CS, section B2.7.1, page 108 *ITT population excluding prior SOF+ RBV ± peg-IFN failures				

ERG comment: As can be seen from Table 4.8, numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each group. Only four out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC, GT2/TN/NC and GT3/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

4.2.2 Health-related quality of life

[redacted] In ENDURANCE-1, '[redacted]' (G/P vs Placebo) and in ENDURANCE-3 '[redacted]' (G/P vs SOF/DCV). In studies without a comparator, many treatment arms [redacted], according to the company.

4.2.3 Subgroup analyses

Subgroup analyses are described in section B2.8 (pages 128-129) of the CS and Appendix E (CS Appendix, pages 385-392). Basic results presented above are already reported by genotype, for people with and without cirrhosis and based on previous treatment (naïve or experienced). Additional subgroups mentioned in the scope are:

- co-infection with HIV
- previous treatment received (with or without DAA-containing regimens)
- people who have received treatment before liver transplantation, and those who have received it after liver transplantation

- response to previous treatment (non-response, partial response, relapsed)
- people who are intolerant to or ineligible for interferon treatment
- people with and without renal impairment

From these subgroups, the company provided results for people co-infected with HIV (EXPEDITION-2). No results are provided for any of the other subgroups that were used in the economic model.

4.2.4 Adverse events

The summary of the safety profile for G/P in the SmPC[11] shows that in patients treated for eight, 12 or 16 weeks with compensated liver disease (with or without cirrhosis), based on Phase 2 and 3 studies which evaluated approximately 2,300 patients, the most commonly reported adverse reactions (incidence ≥ 10%) were headache and fatigue. Less than 0.1% of patients treated with G/P had serious adverse reactions (transient ischaemic attack). The proportion of patients treated with G/P who permanently discontinued treatment due to adverse reactions was 0.1%. The type and severity of adverse reactions in patients with cirrhosis were overall comparable to those seen in patients without cirrhosis.[11]

The most commonly reported adverse reactions identified in patients treated with G/P are reported in Table 4.9. The adverse reactions are listed below by body system organ class and frequency.

Table Error! No text of specified style in document.**.2: Adverse reactions identified with G/P**

Frequency	**Adverse reactions**
Nervous system disorders	
Very common	headache
Gastrointestinal disorders	
Common	diarrhoea, nausea
General disorders and administration site conditions	
Very common	fatigue
Common	asthenia
Source: Glecaprevir & Pibrentasvir (Maviret) Draft SPC_26-06-2017[11] Very common: ≥ 1/10), common: ≥ 1/100 to < 1/10)	

Adverse events (AEs) in the CS are reported in four groups. First, AEs from a placebo-controlled study (ENDURANCE-2); second, AEs from an active-controlled study (ENDURANCE-3); third, AEs from all randomised patients from 21 arms of the Phase II/III studies who received at least one dose of G/P 300 mg/120 mg OD without RBV; and fourth, AEs from a study including patients with chronic kidney disease (CKD Stage 4/5; EXPEDITION-4).

Placebo-controlled study: ENDURANCE-2

In the placebo-controlled analysis set, 302 (202 G/P, 100 placebo) patients received at least one dose of study drug in ENDURANCE-2. Patients were genotype GT2, NC, TN or TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN. Treatment was 12 weeks of G/P at a dose of 300 mg/120 mg. Adverse events from ENDURANCE-2 are reported in Table 4.10.

Table 4.3: ENDURANCE-2 and ENDURANCE-3 adverse events summaries

Adverse events, n (%)	ENDURANCE-2		ENDURANCE-3	
	G/P (300 mg/ 120 mg), 12 weeks (N=202)	Placebo 12 weeks (N=100)	G/P (300 mg/ 120 mg) 12 weeks (N=233)	SOF + DCV 12 weeks (N=115)
≥1 AE	131 (64.9)	58 (58.0)	177 (76.0)	80 (69.6)
≥1 treatment-related AE	[redacted]	[redacted]	112 (48.1)	50 (43.5)
Grade 3 or 4 AE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3/4 AEs				
Alanine aminotransferase increased	[redacted]	[redacted]	NR	NR
Ankle fracture	[redacted]	[redacted]	NR	NR
Aspartate aminotransferase increased[a]	[redacted]	[redacted]	NR	NR
Bile duct stone[c]	[redacted]	[redacted]	NR	NR
Gamma-glutamyltransferase increased[a]	[redacted]	[redacted]	NR	NR
Haemorrhoids	[redacted]	[redacted]	NR	NR
Joint dislocation[b]	[redacted]	[redacted]	NR	NR
Pulmonary pain	[redacted]	[redacted]	NR	NR
Neutropaenia	[redacted]	[redacted]	NR	NR
≥1 treatment-related SAE	NR	NR	NR	NR
Deaths	NR	NR	NR	NR
Discontinuation due to AEs	NR	NR	1	NR
Common AEs[†]				
Headache	24 (11.9)	12 (12.0)	60 (25.8)	23 (20.0)
Fatigue	23 (11.4)	10 (10.0)	44 (18.9)	16 (13.9)
Insomnia	NR	NR	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	32 (13.7)	15 (13.0)
Oropharingeal pain	[redacted]	[redacted]	NR	NR
Nasopharyngitis	NR	NR	[redacted]	[redacted]
Upper respiratory infection	NR	NR	[redacted]	[redacted]
Irritability	NR	NR	NR	NR
Cough	NR	NR	NR	NR
Pruritus	[redacted]	[redacted]	NR	NR
Dyspepsia	NR	NR	NR	NR
Back pain	NR	NR	NR	NR
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	NR	NR
Constipation	NR	NR	NR	NR

Table 4.4: Overview of AEs (EXPEDITION-4)

	EXPEDITION-4, n (%) (N=104)
Any AE	74 (71.2)
Any DAA-related AE[a,b]	[redacted]
An AE Grade ≥3	[redacted]
Any DAA-related AE Grade ≥3[a,b]	[redacted]
Any SAE	25 (24.0)
Any DAA-related SAE[a,b]	0
Discontinuation of study drug due to:	
Any AE	4 (3.8)
Any DAA-related AE[a,b]	[redacted]
Any fatal AE	[redacted]
All deaths[c]	1 (1.0)

Source: CS Appendix F, Table 206, page 165
[a]DAAs = GLE, PIB, or G/P; [b]Investigator assessment; [c]Includes nontreatment-emergent deaths
AE = adverse event; DAA = direct-acting antiviral agent; G/P = glecaprevir/pibrentasvir; GLE = glecaprevir; PIB = pibrentasvir; SAE = serious adverse event

Among patients in EXPEDITION-4, the most frequently reported (≥10.0% of patients) AEs were pruritus, fatigue, and nausea (see Table 4.13).

Table 4.5: Treatment-emergent adverse events reported in ≥ 5.0% of patients

MedDRA 19.0 Preferred Term	EXPEDITION-4, (N = 104), n (%)
Any adverse event	[redacted]
Pruritus	[redacted]
Fatigue	[redacted]
Nausea	[redacted]
Asthenia	[redacted]
Diarrhoea	[redacted]
Decreased appetite	[redacted]
Headache	[redacted]
Vomiting	[redacted]
Dizziness	[redacted]
Dyspnoea	[redacted]

Source: CSR, Table 25, page 138[59]
EXPEDITION-4: G/P, 300 mg/120 mg QD for 12 weeks
MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily

Of the patients in EXPEDITION-4 experiencing DAA-related events (N=[redacted]), [redacted] ([redacted]%) had events of maximum severity of Grade 1 (mild), [redacted] ([redacted]%) had a maximum severity of Grade 2, and [redacted] ([redacted]%) had a maximum severity of Grade 3.

[redacted]

[redacted]

In CERTAIN-1, the primary efficacy analysis was the percentage of GT1-infected NC patients in the ITT population of sub-study 1 without Y93H polymorphisms who achieved SVR12. This was 99.1% (two-sided 95% CI 97.2% to 100.0%) following eight weeks of treatment with G/P, and 100% [redacted] following 12 weeks of treatment with OBV/PTV/RTV. Further results for this study are not reported in the company submission. The CSR shows that a SVR12 rate of [redacted] was achieved in HCV GT3-infected patients with compensated cirrhosis or without cirrhosis and with or without prior pegylated IFN/ribavirin experience who were treated with 12 weeks of G/P.[64] [redacted].

The fixed-dose combination of G/P 300 mg/120 mg QD administered for eight and 12 weeks was well tolerated by Japanese patients including those without cirrhosis, with compensated cirrhosis, and with severe renal impairment, including those on dialysis. A similar safety profile was observed between HCV GT1-infected, DAA treatment-naïve, Japanese patients treated with either G/P 300 mg/120 mg QD administered for eight weeks or OBV/PTV/RTV QD for 12 weeks. Overall, among patients treated with G/P, the most common (≥ 5.0% of patients) TEAEs were nasopharyngitis, pruritus, and headache.[64]

4.5.2 CERTAIN-2

The CERTAIN-2 trial (NCT02723084) was a Phase III, randomised, open-label, multicentre study to evaluate the efficacy of G/P in Japanese NC adults with chronic GT2 HCV infection.[64, 67-69] The objectives of the study were to determine the safety and efficacy of G/P treatment.

GT2-infected NC DAA-TN patients were randomised at a 2:1 ratio to receive G/P (300 mg/120 mg) for eight weeks or SOF + RBV for 12 weeks. 136 patients were enrolled. The primary efficacy endpoint tested the non-inferiority of the SVR12 rate in the eight-week G/P arm to the 12-week SOF + RBV arm. The secondary efficacy endpoints were in line with CERTAIN-1.

In CERTAIN-2, the SVR rate among GT2-infected DAA-TN patients without cirrhosis 12 weeks after treatment with G/P for eight weeks was 97.8% (two-sided 95% CI 94.7% to 100.0%), and 93.5% [redacted] with SOF + RBV for 12 weeks. Further results for this study are not reported in the company submission.

The fixed dose combination of G/P 300 mg/120 mg QD administered for eight weeks was well tolerated by Japanese patients with HCV GT2 infection without cirrhosis. Patients treated with G/P treatment had fewer overall TEAEs and TEAEs related to treatment compared to SOF + RBV treatment. Patients treated with SOF + RBV had higher rates of anemia, hyperbilirubinemia, and hyperuricemia. Overall among patients treated with G/P, the most common (≥ 5% of patients) TEAEs were nasopharyngitis, headache, and malaise. No TEAE related to treatment was reported in > 5% of patients treated with G/P. The most common (≥ 5% of patients) TEAEs reported among patients receiving SOF + RBV were anemia, blood bilirubin increased, malaise, nasopharyngitis, nausea, stomatitis, and hyperuricemia. TEAEs related to SOF + RBV reported in > 5% of patients included anemia and blood bilirubin increased. The higher rates of these events related to SOF + RBV are likely due to the effect of RBV.[69]

4.6 Conclusions of the clinical effectiveness section

The conclusion from the G/P studies is that G/P has high SVR rates in all genotypes. In addition, G/P has a relative favourable safety and tolerability profile. However, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each subgroup. Only four out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC, GT2/TN/NC and GT3/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

In line with previous approaches accepted by NICE,[176] the company did not include onward transmission and the probability of re-infection in their cost effectiveness model. The ERG agrees with the company that modelling onward transmission would not fit into a common Markov model. However, re-infection probabilities have been excluded from the model without any proper justification. The company claims (on page 145 in the CS) that including onward transmission in the model is likely to result in lower ICERs for active treatments,[2] in particular, for those that are most effective and for which onward transmission would be most reduced. In contrast, re-infection is likely to result in higher ICERs for active treatments since patients who achieved SVR would be in risk of advancing to more severe health states without the possibility of re-achieving SVR (given that subsequent therapies are not included in the model). The company also refers to Madin-Warburton et al. 2016 where it is shown that "*there is a net positive impact on cost effectiveness in a dynamic transmission model for treatment of HCV infection of incorporating both re-infection and onward transmission"*.[179] Based on these, the company concluded (on page 145 in the CS) that their model "*may represent a conservative approach that under-estimates the cost effectiveness of active treatments including G/P*".[2] While this conclusion might be correct, the ERG considers that it is not possible to determine the extent to what this approach is indeed conservative or not. In response to the clarification letter, the company performed a scenario analysis showing for one subgroup that the addition of these reinfection probabilities had only minimal impact on the results.

5.2.3 Population

The patient population considered in the company's economic analyses was adults with CHC. Results are presented for 26 different subgroups, which are characterised by HCV genotype, treatment history and fibrosis status. There are six different HCV genotypes (GT1-GT6), each with different characteristics (see also Section 2 of this report). Treatment history distinguishes between treatment-naïve and treatment-experienced patients where the latter are defined as patients who have not adequately responded to prior IFN/RBV-based treatment with or without SOF. This is in line with the clinical trial programme of G/P (see Section B.2 in the CS).[2] Fibrosis status considers non-cirrhotic patients (i.e. patients with METAVIR score F0-F3) and patients with compensated cirrhosis (i.e. patients with METAVIR score F4). Analyses for IFN-ineligible versus IFN-eligible patients are conducted for GT2 treatment-naïve patients only. However, it should be noted that the only differences between the IFN-eligible and IFN-ineligible patients are the comparators considered for the economic analyses, i.e. the SVR or AE rates are not adjusted according to IFN-eligibility. Furthermore, GT1a and GT1b subgroups are not differentiated in the company's model. A summary of the subgroups included in the CS is presented in Table 5.3.

Table 5.6: Population subgroups considered in the company's economic analyses

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	✓	✓	✓	✓
GT2	IFN-eligible: ✓ IFN-ineligible: ✓	IFN-eligible: ✓ IFN-ineligible: ✓	✓	✓
GT3	✓	✓	✓	✓
GT4	✓	✓	✓	✓
GT5	✓	✓	✓	✓

The company did not consider any treatment continuation rules for G/P or any relevant comparators. Although NICE guidance recommends SOF + DCV for GT3 NC patients with significant fibrosis only, the company took a pragmatic approach and included this treatment as a comparator for all GT3 NC patients.

5.2.5 Perspective, time horizon and discounting

The cost effectiveness analyses performed by the company adopted the perspective of the NHS/PSS. A discount rate of 3.5% was applied for both costs and utilities. A 70-year time horizon with an annual cycle length was assumed in the cost effectiveness model.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness parameters for the model were derived from the trial data described throughout Section 4 of this report. As explained in Section 5.2.2, two main types of transition probabilities can be distinguished in the model: SVR rates and natural disease progression transition probabilities. These are discussed in more detail below.

Sustained virologic response rates

SVR rates were obtained from clinical trial data. These were used to estimate the transition probabilities from baseline health states (mild fibrosis, moderate fibrosis or CC) to the corresponding "recovered" health state after successful treatment. In particular, the SVR rates (defined as HCV RNA <LLOQ) observed at 12 weeks after the end of treatment on the ITT population (denoted by SVR12) from the company and comparator clinical trials were used directly in the model. These are presented in Table 4.16 of this report. SVR rates are further stratified by fibrosis severity (NC [F0–F3] and CC [F4]) and HCV genotype (GT1 to GT6). Since in most of cases available data did not report different SVR rates for mild (F0-F1) and moderate (F2-F3) fibrosis, the available NC SVR rate was applied for both the mild and moderate fibrosis health states. Only for SOF/LDV in GT1 TN patients, SVR rates were obtained separately for patients with mild and moderate fibrosis.

ERG comment: The model uses the SVR12 rates obtained in RCTs with the various treatment options as model input for treatment effectiveness. As also discussed in Section 4 of this report the main concern is that data for SVR12 were taken from single arms. Therefore, the comparisons for SVR12 rates between G/P and comparators rely on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. The limitations of this input data necessarily lead to non-robust cost effectiveness outcomes.

In addition, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each subgroup. Only four out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC, GT2/TN/NC and GT3/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

Natural disease progression transition probabilities

Natural disease progression transition probabilities were derived from the literature. These were categorised in four different groups: fibrosis progression, non-fibrosis progression, liver transplantation and liver-related mortality. A brief description of each category and a summary of the annual transition probabilities used in the economic model are given below.

ERG comment: Using utilities derived from the literature[153] is consistent with the approach used in previous STAs.[25, 26, 195, 197] However, it also means that in this STA, as well as some of the previous STAs, utilities derived from RCTs have not been taken into account in the base-case. In the CS it is argued that UK patients represented only a small percentage of the total enrolled patient sample in the various G/P RCTs and that it was therefore felt that these utilities would not be representative of the UK patients suffering with CHC. A similar justification was given in the STA of EBR/GZR.[147] However, the ERG questions to what extend utility values published in 2006 (originating from EQ-5D questionnaires completed in 2002),[153] i.e. before the DAA-era, can be seen as representative of UK patients currently suffering with CHC.

As the RCT-based utilities are higher than those observed in Wright et al. 2006,[153] with smaller differences between F0-F1, F2-F3, and F4, and smaller differences between states with and without a SVR, it is relevant to assess the impact of changing the source of the health state utility values. This scenario analysis has been provided in the CS, and the results are presented in Section 5.3. There it can be seen that these RCT utility values lead to a higher number of QALYs per treatment, without really altering the conclusions regarding cost effectiveness.

From the RCT-based utility values as presented in Table 117 from the CS,[2] it can be seen that the difference in utility of a health state with or without SVR ranges from 0.025 to 0.029, substantially lower than the increment of 0.05 applied by the company.[153] This raises the question if the utility gain observed in Wright et al. 2006 can still be considered as a valid estimate.[153] The ERG therefore requested in their clarification letter (question B11) that the company would perform a scenario analysis with the SVR-gain set to 0, as an extreme scenario. [13] Although the company explained how to do such scenario analysis in the electronic model, they did not provide the results of that scenario analysis. Hence, the ERG ran the scenario and its results are presented in Section 5.3, showing only a minimal impact on the results.

The impact of receiving treatment on health-related quality of life was taken into account in the company model using utility increments and decrements. Note that these changes in utility were only applied while patients are on treatment but not through the whole model's time horizon. Conceptually, the ERG agrees with this approach as it takes into account both the impact of a quick response to treatment and the impact of adverse events. However, most of these adjustment estimates were based on the same studies as the estimates of SVR rates and AE rates, implying that all comments regarding those (see Section 4.6) apply here as well. Therefore, the ERG requested in their clarification letter (question B11) that the company would perform a (worst case) scenario analysis in which no utility adjustments would be applied.[13] However, the company opted not to provide the results of such analysis and instead only described which changes had to be made to run the analysis. In Section 5.3 the results of the scenario analysis as run by the ERG are presented, showing only a small impact on the results.

5.2.9 Resources and costs

In the CS the costs for the clinical management of CHC are made up of two main components: 1) Health state costs and 2) treatment-related costs.

Health state costs capture the average medical costs in a specific health state. Costs include those associated with the management of progressive liver disease (in patients who do not respond to treatment) and with post-treatment surveillance following treatment cessation and achievement of SVR.

Treatment-related costs consist of drug acquisition costs multiplied by the mean treatment duration from trials, costs associated with on-treatment monitoring for response, and costs of treating adverse events to treatment.

Observational data regarding resource use for adverse events would be needed to reduce the uncertainty that currently exists. However, from the lack of mentioning of AE costs in the tornado diagrams reporting the DSA (CS Appendix L.1.3) it can be deducted that even when adverse event costs are altered by 50%, they have an almost negligible impact on the results.[16]

5.2.10 Cost effectiveness results

Cost effectiveness results were presented incrementally including all relevant comparators for the different subgroups considered in the analyses. Subgroups were characterised by genotype (GT1 – GT6), treatment history (treatment-naïve or treatment-experienced) and cirrhosis status (non-cirrhotic or compensated cirrhosis). Furthermore, GT2 treatment-naïve patients were also subdivided by IFN-eligibility. This resulted in 26 subgroups in total as reported in Table 5.3 in Section 5.2.3.

Base-case incremental cost effectiveness analysis results

The results summarised in this section are sourced from Appendix B14 in the clarification responses.[17] These were provided by the company after it was discovered during the clarification phase (Question B14 in the clarification letter[17]), that the results reported in the CS did not match those obtained from the submitted economic model. In these analyses, list prices were used for G/P and all comparators.

Table 5.17 below provides an overview of the (list price) base-case cost effectiveness results per subgroup. In the CS, results often refer to both the £20,000 and £30,000 cost per QALY threshold, which might be leading to some confusion, given the vast amounts of results that need to be presented. Given the high level of uncertainty associated with some of the efficacy input parameters of the model (due the small sample sizes on which they are based), the ERG chose to describe the cost effectiveness results in this section based on the £20,000 threshold.

It was observed that, for non-cirrhotic patients, G/P was always cost effective except for the following two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For seven of the 13 subgroups where G/P was not considered cost effective as it was dominated, G/P could be considered as approximately equivalent (same QALYs at only slightly higher costs, i.e. max £200) to the most cost-effective comparator, SOF/VEL. This is indicated with shaded cells in Table 5.17. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was nearly equivalent to SOF/VEL, the most cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).

For patients with compensated cirrhosis, the results for G/P were the same as in GT4.

5.2.11 Sensitivity analyses

Sensitivity analyses were undertaken in the 26 patient subgroups described in Section 5.2.3 of this report. Due to the large number of subgroups and comparators within each subgroup, the company judged it unfeasible to perform PSA/DSA for all treatment comparisons in all patient subgroups (cf. pp. 217 and 219 in the CS).[2] Thus, for each subgroup a comparison of G/P to a single comparator treatment was chosen. The comparator was selected as the one against which G/P had the lowest incremental net monetary benefit when valuing a QALY at £20,000. The comparators used by the company in the PSA/DSA are summarised per subgroup in Table 5.18.

Table 5.7: Comparators used for PSA/DSA analyses

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	SOF/LDV	EBR/GZR	OBV/PTV/RTV + DSV	SOF/VEL
GT2	IFN-eligible: peg-IFN + RBV IFN-ineligible: SOF + RBV	IFN-eligible: SOF/VEL IFN-ineligible: SOF/VEL	SOF/VEL	SOF/VEL
GT3	SOF/VEL	SOF/VEL	SOF + peg-IFN + RBV	SOF/VEL
GT4	OBV/PTV/RTV	OBV/PTV/RTV	OBV/PTV/RTV	OBV/PTV/RTV
GT5	SOF/VEL	SOF/VEL	SOF/VEL	SOF/VEL
GT6	SOF/VEL	SOF/VEL	SOF/VEL	SOF/VEL

Source: Table 113 in the CS.[2]
DSA = deterministic sensitivity analysis; DSV = dasabuvir; EBR = elbasvir; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; PSA = probabilistic sensitivity analysis; PTV = paritaprevir; peg-IFN = pegylated IFN; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; VEL = velpatasvir

ERG comment: The ERG considers that choosing a single comparator in a PSA is methodologically incorrect and the interpretation of the results can be potentially misleading. In general, when more than two treatments have a positive cost effectiveness probability at a certain cost effectiveness threshold, restricting the analysis to two treatments only is likely to overestimate the cost effectiveness probability of the most cost effective treatment. Therefore, PSA with multiple comparators should have been performed.

Probabilistic sensitivity analysis

The company distinguished between treatment-specific and non-treatment specific input parameters. The first group included SVR rates, AE rates and treatment-related utility change. Treatment-specific input parameters were varied when possible using the 95% confidence intervals observed in the clinical trials. This was the case for SVR and AE rates, which were assumed to follow a Beta distribution, with the input parameters given by the trial subgroup sample size and percentage of patients achieving SVR or with an AE in that subgroup. SVR rates were summarised in Table 4.16 and AE rates in Table 5.9 and 5.10. Due to the lack of data, only for G/P was the treatment-related utility change (see Table 5.12)

of subgroups included in the economic analyses, the adjustments that needs to be made for each of them (e.g. selecting the appropriate comparators) and the lack of time, the ERG considered that the aspects mentioned above could have been corrected in the model to facilitate its validation and to avoid an unnecessary burden on the ERG.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

In this section, the ERG conducted additional scenario analyses on the company base-case to explore the uncertainty around the assumptions taken in the company's base-case analysis. The ERG refrained from setting a preferred base-case, despite the concerns about the uncertainty surrounding SVR rates for the intervention and its comparators, which are caused by small sample sizes for some groups (e.g. n=2) as well as the method used to compare the effectiveness between treatments (naïve indirect comparison). The impact of including uncertainty appropriately for 100% SVR rates and 0% AE rates was already addressed in section 5.2.11. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses.

The following exploratory scenarios were conducted:

- No utility gain in SVR
- No treatment effect in utility
- Age based utility decrement
- Alternative transition probability inputs for fibrosis states
- Non-zero re-infection rates

5.3.1 Scenario-1: No utility gain in SVR

In this scenario, it was assumed that after SVR, there is no additional gain in health utility, whereas in the base-case a utility gain of 0.05 was assumed. In this scenario, it was assumed that after SVR, there is no utility gain, whilst in the base-case a utility gain of 0.05 was assumed. The removal of this utility gain has no impact on the ranking of G/P regarding cost effectiveness (yes or no in a subgroup), total costs, and total QALYs; these remain the same as presented in Table 5.17.

5.3.2 Scenario-2: No treatment specific health utility change

In this scenario, it was assumed that there is no treatment-related health utility change whilst on treatment. In the base-case, the values given in Table 5.12 were applied. Removing these utility adjustments had only an impact on the QALY ranking for GT4, GT5 and GT6, for TE NC patients. It had no impact on the ranking of G/P regarding cost effectiveness and total costs.

Table 5.8: G/P cost effectiveness per subgroup, without a treatment-related utility adjustment (based on list price deterministic full incremental results)

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	Compensated cirrhosis	Non-cirrhotic	Compensated cirrhosis
GT1	same as Table 5.17	same as Table 5.17	same as Table 5.17	same as Table 5.17
GT2	IFN-ineligible: same as Table 5.17	IFN-eligible: same as Table 5.17	same as Table 5.17	same as Table 5.17
	IFN-ineligible: same as Table 5.17	IFN-ineligible: same as Table 5.17		
GT3	same as Table 5.17	same as Table 5.17	same as Table 5.17	same as Table 5.17

HCV genotype	Treatment-naïve		Treatment-experienced	
	Non-cirrhotic	**Compensated cirrhosis**	**Non-cirrhotic**	**Compensated cirrhosis**
GT4	same as Table 5.17	same as Table 5.17	G/P cost effective 2nd lowest total costs *highest QALYs (together with SOF/VEL, EBR/GZR and OBV/PTV/RTV + DSV ± RBV)*	G/P not cost effective 4th lowest total costs highest QALYs (together with SOF/VEL and *LDV/SOF*)
GT5	same as Table 5.17	same as Table 5.17	G/P cost effective 2nd lowest total costs *highest QALYs (together with SOF/VEL)*	same as Table 5.17
GT6	same as Table 5.17	same as Table 5.17	G/P cost effective 2nd lowest total costs *highest QALYs (together with SOF/VEL)*	same as Table 5.17

Source: Electronic model.[204]
GT = genotype; IFN = interferon; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); QALY = quality-adjusted life year; SOF = sofosbuvir; VEL = velpatasvir; DSV = dasabuvir; EBR = elbasvir; GZR = grazoprevir; LDV = ledipasvir; OBV = ombitasvir; PTV = paritaprevir; RTV = ritonavir; RBV = ribavirin;

5.3.3 Scenario-3: Age-based utility decrement

In this scenario, age based utility decrements derived from Ara and Brazier 2010[210] were applied. In the base-case, no age based utility decrements were applied. The addition of these age based utility decrements has no impact on the ranking of G/P regarding cost effectiveness, total costs, and total QALYs; these remain the same as presented in Table 5.17.

5.3.4 Scenario-4: Alternative transition probabilities for the fibrosis states

In this scenario, alternative transition probabilities from Grischenko et al. 2009 were applied for the transitions between the fibrosis states.[178] In the base-case transition probabilities from Thein et al. 2008 were used.[158] When compared with the base-case results, the addition of these alternative transition probabilities has no impact on the ranking of G/P regarding cost effectiveness, total costs, and total QALYs; these remain the same as presented in Table 5.17.

5.3.5 Scenario-5: Non-zero re-infection rates

In this scenario alternative probabilities for re-infection from SVR states were incorporated. This scenario was performed by the company in response to the clarification letter for one subgroup, and was repeated by the ERG for all subgroups. The re-infection probability estimate of 0.0033 from Simmons et al. 2016[211] was assumed. In the base-case re-infection probability was assumed to be zero.

5.4 Conclusions of the cost effectiveness section

The ERG considered that the economic model described in the CS meets the NICE reference case to a reasonable extent. While the economic model is in line with the decision problem formulated by the company, it is only partially in line with the scope. Intervention and comparators included in the company's economic analysis were also included in the scope. However, other comparators listed in the NICE scope [1) DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE); 2) IFN with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients); 3) SOF in combination with RBV, with or without IFN (for specific people with GT1 and GT4; as recommended by NICE)] were not included in the company's cost effectiveness analysis because, according to the company, these are not used in current NHS practice. Furthermore, despite being included in the scope, the company did not perform subgroup analyses for patients who are co-infected with HIV and post-liver transplantation. The subgroup of patients who are intolerant to or ineligible for interferon treatment were only considered for GT2 TN patients.

The ERG assessment indicated that the model was presented and reported appropriately except for the sensitivity analyses. The company developed a de novo cost effectiveness model to assess the cost effectiveness of G/P compared to nine different comparators: BSC-watchful waiting, DCV/SOF, DCV/SOF/RBV, EBR/GZR, LDV/SOF, OBV/PTV/DSV+DSV ± RBV, PR, SOF/PR, SOF/RBV and SOF/VEL.

The cost effectiveness analyses performed by the company are in line with previous STAs for HCV treatments. The population considered in the cost effectiveness analyses was sub-divided into 26 different subgroups, where patients were stratified by genotypes (GT1, GT2, GT3, GT4, GT5 and GT6), treatment experience (treatment-naïve and treatment-experienced patients), cirrhosis status (cirrhotic and non-cirrhotic patients) and IFN-eligibility (only for GT2 TN patients).

The cost effectiveness model developed for this submission was a Markov model which consists of 13 health states. Non-cirrhotic patients start from states F0-F3, and cirrhotic patients start from F4. All treatment related outcomes (achieving SVR, treatment related adverse events and discontinuation) occur within the first year of the model. Patients who do not achieve SVR are at risk of progressing to more severe states. Patients who reached F4 can progress to DC and HCC states, which may lead to liver transplantation and liver related death. Liver transplantation state was divided into two categories (first year and later years).

The model uses health state based utilities from the literature (utilities that were used in Wright et al. 2006[153] and Ratcliffe et al. 2002[161]) in line with previous STAs for HCV treatments. A utility increment of 0.05 due to SVR is applied based on Shepherd et al. 2007[154] and Hartwell et al. 2011[155]. Treatment-related health utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events.

List prices were used as treatment costs for G/P and the comparator treatments in the cost effectiveness analysis. Health state costs (disease management costs based on disease stage) and other costs for adverse events were based on literature, expert opinion, UK reference costs and previous appraisals for HCV (especially TA430).

It should be noted that while the current model structure does not allow for sequential treatments, in clinical practice, patients who do not achieve SVR (who do not respond to the therapy or discontinue due to adverse events) or who were re-infected after SVR may receive further lines of treatments.

Onward transmission was not included in the economic model. Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework. Similarly, the company assumed a zero-reinfection probability after reaching SVR and assumed that no natural recovery takes place, despite contrary evidence reported in the clinical literature. However, a scenario analysis by the company showed that the addition of these reinfection probabilities has only minimal impact on the results.

Treatment effectiveness was modelled as the probability of achieving SVR. Other treatment-specific parameters included adverse event rates, treatment duration, and treatment-related utility adjustments. All these parameter estimates were based on naïve indirect comparison of clinical trials assessing the efficacy of G/P and its comparators in the relevant subgroups. The ERG has concerns on the plausibility of this approach, which is not in line with the evidence synthesis best practices and susceptible to bias. Furthermore, some of the SVR rates were derived from very small sample sizes or the effectiveness in a subgroup was assumed to hold in another subgroup. Since SVR probability is the main driver of costs and effectiveness, all these assumptions create a substantial uncertainty on the cost effectiveness of G/P.

Furthermore, it was not clear to the ERG why age-dependent transition probabilities were not updated every year.

The health state utilities from RCTs could have been used by the company in their cost effectiveness analysis instead of the utilities from the literature. The ERG questions to what extend utility values published in 2006 (originating from EQ-5D questionnaires completed in 2002),[153] i.e. before the DAA-era, can be seen as representative of UK patients currently suffering with CHC. Similarly, the RCT-based utility values show a difference in utility with or without SVR ranging from 0.025 to 0.029, substantially lower than the increment of 0.05 applied by the company based on Wright et al. 2006[153] thus raising doubt about the validity of the latter value.

The impact of receiving treatment on QoL during treatment was taken into account in the company model using utility increments and decrements. However, most of these adjustment estimates were based on the same studies as the estimates of SVR rates and AE rates, implying that all comments regarding those (see Section 4.6) apply here as well.

The ERG was unsure about the completeness of the health state cost estimates used in the model, as items such as GP visits and home care costs are not included.

The base-case cost effectiveness results showed that, for non-cirrhotic patients, G/P was always cost effective except for the following two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For seven of the 13 subgroups where G/P was not considered cost effective, as it was dominated, G/P could be considered as approximately equivalent (same QALYs at only slightly higher costs, i.e. max £200) to the most cost-effective comparator, SOF/VEL. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was nearly equivalent to SOF/VEL, the most cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).

7. OVERALL CONCLUSIONS

7.1 Statement of principal findings

Eighty-one publications (reporting on 79 studies) were identified as meeting the eligibility criteria. Fourteen of these publications, representing seven studies, involved G/P. In addition, information on four further clinical studies of G/P in patients with CHC are included in the company submission. These studies were conducted in special populations of patients with HIV co-infection, renal impairment, failure on prior DAAs and a post-transplant population. Finally, the company mentions two trials in Japanese patients with CHC: CERTAIN-1 and CERTAIN-2. These trials are only minimally discussed in the CS and not included in the economic model because "*these two trials were conducted entirely in Japanese patients*" which "*precludes their generalisability to the UK patient population and subsequently their use in the economic model*", according to the company.[2] Apart from these two trials in Japanese patients, none of the included studies presented comparative data for the licensed treatment duration of G/P with any of the comparators.

The G/P studies included patients with all genotypes; treatment-naïve and experienced patient populations; and patients with 'no cirrhosis and compensated cirrhosis'.

When split by cirrhosis status and previous treatment (naïve or experienced), SVR rates were consistently above 90% for all genotypes, except for GT2/TE/NC (in SURVEYOR-II, Part 4; but in SURVEYOR-II, Parts 1 and 2), GT3/TE/CC (in SURVEYOR-II, Part 2; but in SURVEYOR-II, Part 3) and GT6/TN/NC (in SURVEYOR-II, Part 4).

In studies without a comparator, many treatment arms

According to the company, G/P has a favourable safety profile that was similar to placebo and SOF/DCV, and that was similar across durations of eight, 12, and 16 weeks. G/P was well tolerated across a broad and diverse population of patients, including patients with CC, HIV co-infection, and CKD Stage 4/5. Common study adverse drug reactions (ADRs) occurring in ≥5% of patients were headache, fatigue, and nausea. Adverse drug reactions were mostly Grade 1 (mild) in severity. Serious ADRs and ADRs leading to premature study drug discontinuation were rare (≤0.1%).

The results of the company's base-case showed that, for non-cirrhotic patients, G/P was always cost effective except for the following two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For seven of the 13 subgroups where G/P was not considered cost effective, as it was dominated, G/P could be considered as approximately equivalent (same QALYs at only slightly higher costs, i.e. max £200) to the most cost-effective comparator, SOF/VEL. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was nearly equivalent to SOF/VEL, the most cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).

Probabilistic results were reported by the company as the probability that G/P is cost effective against one single comparator for each subgroup at £20,000 and £30,000 thresholds. However, the ERG showed that including all comparators in the PSA could substantially alter the probability that G/P would be cost effective. The result of the deterministic sensitivity analyses showed that in general the ICER was most sensitive to changes in SVR rates. Two scenario analyses conducted by the company first demonstrated how the cost effectiveness of G/P might change after the CMU price agreement (when comparators from other companies were based on list prices). Second, it was shown that using trial based utilities increased total QALY estimates compared to the base-case when literature based utilities were used as input, without really altering the conclusions from the base-case analyses.

The ERG did not present an alternative base-case, since it was not clear that any alternative base-case assumptions regarding point estimates and structure would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses.

In the scenario analyses assumptions surrounding the utility gain due to SVR, impact of the treatment on utility, impact of age on utility were challenged. In addition alternative inputs for transition probabilities in between fibrosis stages and re-infection rates were explored. Even though these scenarios changed the total costs and/or total QALYs estimates, the impact on incremental results were minimal. The cost effectiveness of G/P in each subgroup did not change, hence the cost effectiveness results of the base-case seem to be robust to changes in utility and treatment unrelated clinical model inputs.

The exploratory PSA analyses conducted by the ERG showed that that the inclusion of parameter uncertainty around all SVR and AE rates (which was not included in the company's base-case whenever rates were 100% or 0%) can have a major impact on the G/P cost effectiveness probability for certain subgroups; but also that this impact can go in either direction (although more frequently it decreases the G/P cost effectiveness probability). This was especially striking for GT5 TN NC patients, for whom the company might have overestimated the cost effectiveness probability of G/P by 66 percent. Furthermore, the ERG showed that the PSA outcomes were enormously scattered over the CE plane quadrants for a number of subgroups and illustrated the main limitation of presenting cost effectiveness probabilities only (as in the CS).

7.2 Strengths and limitations of the assessment

The conclusion from the G/P studies is that G/P has high SVR rates in all genotypes. In addition, G/P has a relatively favourable safety and tolerability profile. However, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each group. Only four out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC, GT2/TN/NC and GT3/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators relies on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. In most cases the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.