NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Elbasvir-grazoprevir for treating chronic hepatitis C [ID842]

The following documents are made available to the consultees and commentators:

Contents:

1. **Pre-Meeting Briefing**

2. **Final Scope and Final Matrix of consultees and commentators**

3. **Company submission** from Merck Sharp and Dohme

4. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company response to NICE's request for clarification
   - Company response to questions A5, A7 and A8
   - UK NICE Outcomes – Deferred Arms

5. **Patient group, professional group and NHS organisation submission** from:
   - Hepatitis C Trust
   - British Association for Study of the Liver
   - British Society of Gastroenterology *endorsed by the Royal College of Physicians*
   - UK Clinical Pharmacy Association

6. **Expert statements** from:
   - Dr Sanjay Bhagani – clinical expert, nominated by British HIV Association
   - Professor Graham Foster – NHS commissioning expert, nominated by NHS England
   - Dr Anna Maria Geretti – clinical expert, nominated by Gilead Sciences

7. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

8. **Evidence Review Group report – factual accuracy check**

9. **Evidence Review Group erratum to the ERG report**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Elbasvir-grazoprevir for treating chronic hepatitis C

This premeeting briefing presents:

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

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

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

NICE has recently appraised similar treatments for chronic hepatitis C. Therefore, where possible, this premeeting briefing attempts to highlight the similarities or differences between the evidence for this appraisal and those previously considered by the appraisal committee for the previous appraisals.

Key issues for consideration

Decision problem

- The final scope includes boceprevir and telaprevir as comparators, but the company did not include them as comparators in its submission on the basis that they no longer represent clinical practice following the introduction of the new direct-acting antivirals (DAA). The professional organisations also stated that these treatments are not used in clinical practice. Does the committee agree with the exclusion of these comparators?

Clinical effectiveness

- The robustness of the elbasvir-grazoprevir trial results given the following;
    - Trials were mostly randomised and 4 out of the 7 trials had a comparator arm (3 placebo controlled trials and 1 active controlled with sofosbuvir).
    - Limited data for the genotype 4 population – previously considered by the appraisal committee for similar hepatitis C NICE appraisals.
    - The ERG agreed with the company's assessment that the risk of bias in the trials was generally low.
    - The ERG did not report any specific concerns about the trials.

- What conclusions can be drawn from the results of the network meta-analysis and naïve comparison given the ERG's concerns (see section 5.10 of this document)?

Cost effectiveness

- The committee's views on the appropriateness of the model structure given the ERG's concerns listed in section 6.2 of this document.
- The ERG stated that subgroup analyses should have been presented for people with HIV co-infection, people who are intolerant to or ineligible for interferon treatment, people treated with a DAA versus non-DAA, people with mild disease (F0-F1) and moderate disease (F2-F3). What are the committee's views on the ERG's comments given the following?
    - The company stated that the EASL 2015 guideline recommends the same treatment duration and regimen for HIV co-infection and HCV mono-infection. It also stated that the elbasvir-grazoprevir trials reported comparable SVR results. This has also been discussed in recent hepatitis C NICE appraisals, where the committee did not make different recommendations for HIV co-infection.
    - The company did not give any real justification for not presenting subgroup analysis for people who are intolerant to or ineligible for interferon. Analyses for this subgroup were presented in TA330 (sofosbuvir) and TA364 (daclatasvir), but not in TA363 (ledipasvir-sofosbuvir) and TA365 (ombitasvir-paritaprevir-ritonavir +/- dasabuvir).

The committee did not identify this as a specific concern for TA363 and TA365.

- The company stated that all the treatment experienced patients in the elbasvir-grazoprevir trials received non-DAA treatments and 2 comparator trials present SVRs for DAA-experienced patients

- The committee's views on the assumptions used in the company's model;
    - Clinical input data, given the ERG's concerns about the robustness of the network meta-analysis.
    - Using genotype 1 data as a proxy for genotype 4. Given the limited evidence available for genotype 4, this approach was accepted by the committee in recent hepatitis C NICE appraisals.
    - Source of health state utility values and SVR-related utility increment (Wright et al. 2006 versus clinical trials). For the SVR-related utility increment, the committee previously accepted Wright et al. for most of the recent appraisals. However, for TA365, where trial data was available, the committee concluded that the value would lie between the estimate from the trial and that from Wright et al. 2006, on the basis that the trial values might be under-estimated because they were collected before patients became aware of their SVR status.
    - Including age-based utility decrements, given the ERG's concerns that these could lead to double counting and they were not included in previous hepatitis C NICE appraisals.

- The most plausible cost-effectiveness estimates for elbasvir-grazoprevir using all the relevant confidential price reductions.

1 The technology

Table 1 Details of the technology

Technology	Elbasvir-grazoprevir (Zepatier, Merck Sharp & Dohme). Single fixed-dose combination drug.
Class of drug	Elbasvir is a HCV NS5A inhibitor and grazoprevir is a HCV NS3/4A protease inhibitor.
Administration method	Oral
List price	£12,166.67 per 28-day pack (elbasvir: 50mg, grazoprevir: 100mg)
Commercial price discount	The maximum price payable within NHS Framework Agreements between MSD and CMU is: [redacted] per 28-day pack
Average cost of a course of treatment	12 weeks treatment duration: £36,500 ([redacted] based on maximum price payable within NHS Framework Agreement between MSD and CMU, submitted 11th April 2016).
Marketing authorisation	Positive CHMP opinion for the treatment of chronic hepatitis C (CHC) in adults. The recommendations for the specific genotypes are listed below; • genotype 1a - 12 weeks (16 weeks plus ribavirin should be considered in patients with baseline HCV RNA level >800,000 IU/ml and/or the presence of specific NS5A polymorphisms causing at least a 5-fold reduction in activity of elbasvir to minimise the risk of treatment failure) • genotype 1b - 12 weeks • genotype 4 - 12 weeks (16 weeks plus ribavirin should be considered in patients with baseline HCV RNA level >800,000 IU/ml to minimise the risk of treatment failure
SmPC	Link to report to be updated
EPAR	Link to report to be updated
Abbreviations: CHMP, Committee for Medicinal Products for Human Use; CMU, Commercial Medicines Unit; EPAR, European public assessment report; HCV, hepatitis C virus; MSD, Merck Sharp & Dohme; NHS, National Health Service; NS3/4A, non-structural protein 3/4A; NS5A, non-structural protein 5A; SMPC, summary of product characteristics;	

2 Relevant NICE technology appraisals

Table 2 Relevant technology appraisals and the recommended treatment regimens

TA Number	Technology	Genotype	Subgroup by cirrhotic status and treatment history	Recommendation & (treatment duration)
TA365[a]	OPR + D (3D) (+/- R)	GT1a	NC TN; NC TE	Yes (12 weeks)
			CC TN; CC TE	Yes (24 weeks)
		GT1b	NC TN; NC TE; CC TN; CC TE	Yes (12 weeks)
	OPR (2D) (+ R)	GT4	NC TN; NC TE	Yes (12 weeks)
			CC TN; CC TE	Yes (24 weeks)
TA364[a]	DCV + SOF (+/- R)	GT1	NC TN; NC TE; NC IFN ineligible/intolerant	Yes, only for significant fibrosis (12 weeks)
		GT3	NC IFN ineligible/intolerant	Yes, only for significant fibrosis (12 weeks)
		GT4	NC TE; NC IFN ineligible/intolerant	Yes, only for significant fibrosis (12 weeks)
		GT1, 3 & 4	CC IFN ineligible/intolerant	Yes (24 weeks)
	DCV + PR	GT4	NC TN; NC TE; CC TN; CC TE	Yes, only for significant fibrosis (24 weeks)
TA363	LDV-SOF	GT1	NC TN	Yes (8 weeks)
		GT1 & 4	NC TE	Yes (12 weeks)
			CC TN	Yes (12 weeks)
			CC TE	Yes, if certain clinical criteria are met (12 weeks)
TA331	SMV + PR	GT1 & 4	All	Yes (12 weeks, followed by 12 weeks or 36 weeks PR)

TA330	SOF + PR	GT1	NC TN; NC TE; CC TN; CC TE	Yes (12 weeks)
		GT3	NC TE; CC TN; CC TE	Yes (12 weeks)
		(GT4, 5 & 6) [b]	CC TN; CC TE	Yes (12 weeks)
	SOF + R	GT2	NC TN; CC TN	Yes, only if IFN ineligible or intolerant (24 weeks)
			NC TE; CC TE	Yes (24 weeks)
		GT3	CC TN; CC TE	Yes, only if IFN ineligible or intolerant (24 weeks)
TA253	BOC + PR	GT1	All	Yes
TA252	TVR + PR	GT1	All	Yes
TA200, 106, 75	PR	GT1 – 6	All	Yes

[a] recommended with price discounts agreed with the Commercial Medicines Unit

[b] recommendation based on indirect discrimination of protected groups

Abbreviations: BOC – boceprevir, CC – compensated cirrhosis, D – dasabuvir, DCV – daclatasvir, GT – genotype, LDV – ledipasvir, NC – no cirrhosis, OPR – ombitasvir/paritaprevir/ritonavir, PR – peginterferon + ribavirin, R – ribavirin, SMV – simeprevir, SOF – sofosbuvir, TA – technology appraisal, TE – treatment experienced, TN – treatment naïve, TVR - telaprevir

3 Comments from consultees

3.1 The professional group stated that elbasvir-grazoprevir will provide an additional alternative to the existing all oral combinations for patients with chronic hepatitis C genotype 1 and 4 disease, with treatment choice being predominately based on commissioning guidance and cost. They stated that boceprevir and telaprevir are not used in clinical practice and will not be useful comparators.

3.2 The professional group noted that elbasvir-grazoprevir offered an advantage in patients with renal dysfunction as it has minimal side effects which are an advantage over sofosbuvir-ledipasvir. It was noted that SVR data were good in patients previously treated with an NS3/4 protease inhibitor which is an advantage over Ombitasvir-paritaprevir-ritonavir and dasabuvir. The professional group also noted that elbasvir-grazoprevir did not have to be used with ribavirin in patients with compensated cirrhosis.

3.3 There is no clinical practice data available as the technology is not yet available in the UK. The professional group noted that elbasvir-grazoprevir would be, initially used in secondary care in hepatology, viral hepatitis and co-infection clinics, and that it was not expected that any additional resources or requirements would be needed above what already exists in clinical practice.

4 Decision problem

Table 3 Company's decision problem and deviations from the final scope

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale for any 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.	Grazoprevir-elbasvir	Elbasvir-grazoprevir	In line with the product label
Com.	• BSC • BOC + PR • DCV + PR • DCV + SOF • LDV + SOF • OPR +/- D (3D and 2D) +/- R • PR • SMV + PR • SOF + PR or R • TVR + PR	• BSC • DCV + PR • DCV + SOF • LDV + SOF • OPR +/- D (3D and 2D) +/- R • PR • SMV + PR • SOF + PR or R	BOC and TVR are no longer representative of current clinical practice following the introduction and approval of the newer DAA technologies and [redacted]
Out.	• sustained virological response • development of resistance to grazoprevir-elbasvir • mortality • adverse effects of treatment • health-related quality of life	• sustained virological response • mortality • adverse effects of treatment • health-related quality of life	Resistance was not considered in post hoc analyses and therefore do not support the economic analyses.

Abbreviations: BOC – boceprevir, D – dasabuvir, DCV – daclatasvir, LDV – ledipasvir, OPR – ombitasvir/paritaprevir/ritonavir, PR – peginterferon + ribavirin, R – ribavirin, SMV – simeprevir, SOF – sofosbuvir, TVR - telaprevir

5 Clinical-effectiveness evidence

Clinical trials of elbasvir-grazoprevir

5.1 The company presented 8 clinical trials of elbasvir-grazoprevir (see table 4). Patients in the relevant elbasvir-grazoprevir arms received 12 weeks treatment with follow-up of 24 weeks.

Table 4 Overview of the clinical trials

Trial name	Design	Population	Intervention	Comparator (s)
C-EDGE H2H	Phase III, randomised, open-label, international, multicentre	N=255 GT1a, 1b, 4 HCV TN and TE With or without cirrhosis	N=129 EBR-GZR: 12 wks *GT1a (14%), 1b (81%), 4 (5%)*	N=126 SOF + PR: 12 wks *GT1a (13%), 1b (83%), 4 (4%)*
C-EDGE TN	Phase III, randomised, double-blind and open-label, international, multicentre	N=421 GT1a,1b, 4, 6 HCV TN With and without cirrhosis	N=316 EBR-GZR: 12 wks *GT1a (50%), 1b (42%), 4 (6%), 6 (3%)*	N=105 Placebo: 12 wks, wash-out period: 4 wks; (followed by EBR-GZR: 12 wks) *GT1a (51%), 1b (38%), 4 (8%), 6 (3%)*
C-EDGE CO-STAR	Phase III, randomised, double-blind, international (including UK), multicentre	N=301 GT1, 4, 6 HCV TN With or without cirrhosis Taking opiate-substitution therapy	N=201 EBR-GZR: 12 wks *GT1a (76%), 1b (15%), 4 (6%), 6 (3%)*	N=100 Placebo: 12 wks, wash-out period: 4 wks; (followed by EBR-GZR: 12 wks) *GT1a (75%), 1b (15%), 4 (6%), 6 (4%)*
C-SURFER	Phase III, randomised, double-blind and open-label, international, multicentre	N=224 CKD stage 4 or 5 GT1a, 1b HCV TN and TE With and without cirrhosis	N=111 EBR-GZR: 12 wks *GT1a (48%), 1b (52%)*	N=113 Placebo: 12 wks, wash-out period: 4 wks; (followed by EBR-GZR: 12 wks) *GT1a (52%), 1b (47%), 1*

				other (1%)
C-EDGE TE	Phase III, randomised, open-label, international, multicentre	N=420 GT1a, 1b, 4, 6 HCV TE With and without cirrhosis	N=105 EBR-GZR: 12 wks *GT1a (58%), 1b (32%), 1 other (1%)* N=315 3 other treatment arms (treatment for 16 wks or with ribavirin) not included in the company's analyses	No control arm
C-WORTHY	Phase II, randomised, double-blind and open-label, international, multicentre, 20 treatment arms	N=573 GT1a, 1b, 3 HCV TN and TE With and without cirrhosis HIV co-infection	N=136 (5 arms) (HIV co-infection, n=30) EBR-GZR: 12 wks *GT1a (67%), 1b (32%), 1 other (1%)* N=437 15 other treatment arms not included in the company's analyses	No control arm
C-SCAPE	Phase II, randomised, open-label, international (including UK), multicentre	N=98 GT1, 4, 5, 6 HCV TN Without cirrhosis	N=19 EBR-GZR: 12 wks *GT1 (5%), 4 (53%), 5 (21%), 6 (21%)* N=79 3 other treatment arms not included in the company's analyses	No control arm
C-EDGE CO-INFECTION	Phase III, non-randomised, open-label, international, multicentre	N=218 GT1a, 1b, 4 HCV TN With and without cirrhosis HIV co-infection	N=218 EBR-GZR: 12 wks *GT1a (66%), 1b (20%), 4 (12.8%), 1 other (0.5%)*	No control arm
Abbreviations: CKD – chronic kidney disease; EBR – elbasvir; GT – genotype; GZR – grazoprevir; HCV – hepatitis C virus; N – number; TE – treatment experienced; TN – treatment naïve; wks - weeks				

ERG comments

5.2 The ERG agreed with the company's quality assessment that there was generally low risk of bias in the studies.

Clinical trial results

5.3 Results of the primary outcome of sustained virological response at 12 weeks (SVR12) from the included clinical trials (by genotype, treatment history and cirrhosis status), are reported in tables 28 - 34 (pages 117 – 122) of the company submission and question A7 (pages 50 – 54) of the company's response to clarification. Due to the volume of these results, only the results from the active-controlled study (C-EDGE H2H; irrespective of treatment history and cirrhosis status) are reported in this premeeting briefing document.

Table 5 SVR12 results from C-EDGE H2H trial

Treatment arm	EBR/GZR, 12 wks		SOF+PR, 12 wks		Unadjusted difference in %
	n/N	%	n/N	%	
GT1 and 4	128/129	99.2	114/126	90.5	8.7†
GT1a	18/18	100	17/17	100	0.0 (-18.0, 18.9)
GT1b	104/105	99	94/104	90.4	8.7 (3.2, 16.0)
GT4	6/6	100	3/5	60	40 (-10.9, 78.1)

Source: ERG report, page 47 (table 4.7)
Abbreviations: EBR – elbasvir; GT – genotype; GZR – grazoprevir; PR – peginterferon plus ribavirin; SOF – sofosbuvir; wks - weeks
† P<0.001

5.4 The company could not perform a meta-analysis of the trials because only one trial had an active comparator.

ERG comments

5.5 The ERG commented that elbasvir-grazoprevir has high SVR rates, especially for patients with genotype 1a and 1b HCV. It agreed with the company's rationale for not performing a meta-analysis of the trials. In addition, the ERG stated that there is too much heterogeneity between the study populations to perform a reliable meta-analysis.

Indirect evidence

Network meta-analysis

5.6 The company presented network meta-analysis to provide comparative estimates of sustained virological response (SVR) and safety outcomes for elbasvir-grazoprevir and the relevant comparators included in the final scope (except for boceprevir and telaprevir), using evidence from 40 clinical trials. The trials included for each population by genotype, cirrhosis status and treatment history are presented on pages 124 – 126 of the company submission. In the absence of subgroup information for some of the trials, the company made some assumptions to allow for comparisons to be made. For example, genotype 1 data was used for genotype 4 for some treatment regimens in the absence of relevant genotype 4 data. Full details of the assumptions made in the network meta-analysis are presented on page 128 of the company submission.

5.7 For each non-comparative trial in the network meta-analysis, an imputed peginterferon plus ribavirin arm was created, estimated from the peginterferon plus ribavirin arm of comparative trials. The company stated that this approach has been presented at the 2015 ISPOR conference in Milan and has also been used by the Canadian Agency for Drugs and Technologies in Health for their review of treatment for hepatitis C and by the World Health Organisation to inform their 2016 hepatitis C treatment guidelines.

Naïve comparisons

5.8 The company performed naïve comparisons by pooling individual arms of included studies and comparing them directly with each other.

Indirect evidence results

5.9 The company stated that naïve comparison is the least robust way of comparing treatments across trials; therefore only results from the network meta-analysis are presented (see tables 6, 7 and 8 below). The naïve comparison results are presented alongside the network meta-

analysis results in tables 38 – 49 (pages 132 – 139) of the company submission.

Table 6 Network meta-analysis SVR results (random effects): Genotype 1a

Treatment Naive				
Treatment (weeks)	**no cirrhosis**		**cirrhosis**	
	Pooled SVR (95% CI)	**RR (95% CI)**	**Pooled SVR (95% CI)**	**RR (95% CI)**
EBR-GZR (1-12)	96.72 (95.04, 98.40)	--	96.23 (92.15, 100.00)	--
PR (1-48)	49.96 (46.16, 53.77)	**1.86 (1.70, 2.03)**	34.00 (17.68, 50.31)	**2.68 (2.00, 3.80)**
SMV+PR (1-12), PR (13-24) or PR (13-48)	81.76 (78.50, 85.03)	**1.20 (1.09, 1.42)**	60.51 (46.72, 74.31)	**1.50 (1.06, 3.90)**
SOF+PR (1-12)	97.61 (90.34, 100.00)	1.05 (0.95, 1.46)	80.00 (55.21, 100.00)	1.18 (0.96, 7.19)
LDV/SOF (1-8, 1-12)	92.98 (89.15, 96.81)	1.01 (0.95, 1.16)	97.15 (91.65, 100.00)	1.00 (0.92, 1.11)
3D+R (1-12, 1-24)	96.10 (94.39, 97.81)	0.98 (0.93, 1.03)	92.86 (86.11, 99.60)	1.04 (0.94, 1.78)
DCV+SOF (1-12)	96.67 (92.12, 100.00)	0.98 (0.93, 1.13)	--	--
Treatment experienced				
Treatment (weeks)	**no cirrhosis**		**cirrhosis**	
	Pooled SVR (95% CI)	**RR (95% CI)**	**Pooled SVR (95% CI)**	**RR (95% CI)**
EBR-GZR (1-12)	92.65 (85.59, 99.72)	--	91.14 (81.32, 100.00)	--
PR (1-48)	38.05 (29.10, 47.00)	**2.28 (1.68, 2.95)**	26.32 (6.52, 46.12)	**4.03 (2.23, 6.79)**
SMV+PR (1-12), PR (13-24) or PR (13-48)	80.09 (74.71, 85.48)	1.13 (0.87, 2.55)	74.36 (60.65, 88.06)	1.30 (0.79, 17.76)
SOF+PR (1-12)	79.93 (70.44, 89.42)	1.12 (0.86, 2.17)	71.43 (47.76, 95.09)	1.33 (0.77, 26.22)
LDV/SOF (1-12)	98.26 (96.45, 100.00)	0.96 (0.76, 1.04)	98.48 (94.64, 100.00)	0.99 (0.63, 1.22)
3D+R (1-12, 1-24)	96.58 (93.88, 99.28)	0.96 (0.76, 1.07)	95.38 (90.28, 100.00)	1.00 (0.66, 3.14)
DCV+SOF (1-12)	100.00 (29.10, 100.00)	0.97 (0.77, 1.37)	--	--

Source: Company submission (tables 38 – 41, pages 132 – 134), ERG report (table 4.15, page 60)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00)

Abbreviations: DCV, daclatasvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; PR, peginterferon and ribavirin; R, ribavirin; RR, relative risk; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response

Table 7 Network meta-analysis SVR results (random effects): Genotype 1b

Treatment Naive				
Treatment (weeks)	**no cirrhosis**		**cirrhosis**	
	Pooled SVR (95% CI)	**RR (95% CI)**	**Pooled SVR (95% CI)**	**RR (95% CI)**
EBR-GZR (1-12)	98.27 (96.59, 99.94)	--	100.00 (17.68, 100.00)	--
PR (1-48)	49.96 (46.16, 53.77)	**1.92 (1.67, 2.25)**	34.00 (17.68, 50.31)	**2.89 (2.11, 4.25)**
SMV+PR (1-12), PR (13-24) or PR (13-48)	81.76 (78.50, 85.03)	**1.24 (1.11, 1.53)**	60.51 (46.72, 74.31)	**1.58 (1.06, 5.45)**
SOF+PR (1-12)	96.76 (92.29, 100.00)	1.00 (0.97, 1.09)	91.67 (76.03, 100.00)	1.09 (0.99, 4.37)
LDV/SOF (1-8, 1-12)	97.67 (93.17, 100.00)	1.02 (0.97, 1.27)	97.15 (91.65, 100.00)	1.01 (0.96, 1.16)
3D+/-R (1-12)	98.84 (97.62, 100.00)	0.99 (0.96, 1.02)	100.00 (96.83, 100.00)	1.01 (0.97, 1.62)
DCV+SOF (1-12)	100.00 (46.16, 100.00)	1.00 (0.97, 1.50)	--	--
Treatment experienced				
Treatment (weeks)	**no cirrhosis**		**cirrhosis**	
	Pooled SVR (95% CI)	**RR (95% CI)**	**Pooled SVR (95% CI)**	**RR (95% CI)**
EBR-GZR (1-12)	99.12 (95.12, 100.00)	--	100.00 (6.52, 100.00)	--
PR (1-48)	38.05 (29.10, 47.00)	**2.58 (2.04, 3.32)**	26.32 (6.52, 46.12)	**3.58 (2.10, 6.13)**
SMV+PR (1-12), PR (13-24) or PR (13-48)	80.09 (74.71, 85.48)	1.22 (0.98, 5.25)	74.36 (60.65, 88.06)	1.27 (0.84, 17.95)
SOF+PR (1-12)	84.68 (73.04, 96.32)	1.16 (0.97, 3.37)	50.00 (15.35, 84.65)	1.60 (0.93, 55.93)
LDV/SOF (1-12)	98.26 (96.45, 100.00)	1.00 (0.89, 1.09)	98.48 (94.64, 100.00)	1.00 (0.70, 1.20)
3D+R (1-12)	100.00 (29.10, 100.00)	0.99 (0.89, 1.21)	97.83 (93.61, 100.00)	1.02 (0.75, 4.08)
DCV+SOF (1-12)	100.00 (95.12, 100.00)	1.00 (0.90, 1.79)	--	--

Source: Company submission (tables 42 – 45, pages 135 – 137), ERG report (table 4.16, page 61)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00)

Abbreviations: DCV, daclatasvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; PR, peginterferon and ribavirin; R, ribavirin; RR, relative risk; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response

Table 8 Network meta-analysis SVR results (random effects): Genotype 4

Treatment Naive				
Treatment (weeks)	**no cirrhosis**		**cirrhosis**	
	Pooled SVR (95% CI)	**RR (95% CI)**	**Pooled SVR (95% CI)**	**RR (95% CI)**
EBR-GZR (1-12)	96.97 (91.54, 100.00)	--	100.00 (0.00, 100.00)	--
PR (1-48)	39.47 (23.93, 55.01)	**2.36 (1.57, 3.65)**	25.00 (0.00, 67.43)	**5.26 (2.11, 9.85)**
SMV+PR (1-12), PR (13-24) or PR (13-48)	84.38 (71.79, 96.96)	1.09 (0.84, 29.18)	66.67 (13.32, 100.00)	1.23 (0.55, 82.71)
SOF+PR (1-12)	--	--	83.77 (75.45, 92.09)	1.11 (0.50, 2.17)
LDV/SOF (1-8, 1-12)	--	--	97.15 (91.65, 100.00)	1.00 (0.44, 1.21)
2D+R (1-12, 1-24)	100.00 (23.93, 100.00)	1.00 (0.79, 4.62)	97.87 (93.75, 100.00)	1.02 (0.49, 3.23)
DCV+SOF (1-12),	--	--	--	--
DCV+PR 1-24 or DCV+PR 1-24, PR 25-48	71.01 (60.31, 81.72)	1.35 (0.90, 59.42)	77.78 (50.62, 100.00)	1.25 (0.57, 18.75)
Treatment experienced				
Treatment (weeks)	**no cirrhosis**		**cirrhosis**	
	Pooled SVR (95% CI)	**RR (95% CI)**	**Pooled SVR (95% CI)**	**RR (95% CI)**
EBR-GZR (1-12)	100.00 (29.10, 100.00)	--	66.67 (28.95, 100.00)	--
PR (1-48)	38.05 (29.10, 47.00)	2.59 (0.91, 3.94)	26.32 (6.52, 46.12)	2.47 (0.06, 5.67)
SMV+PR (1-12), PR (13-24) or PR (13-48)	63.64 (49.42, 77.85)	1.43 (0.55, 26.21)	46.43 (27.96, 64.90)	1.45 (0.04, 30.13)
SOF+PR (1-12)	--	--	64.61 (45.07, 84.15)	0.96 (0.03, 6.40)
LDV/SOF (1-12)	98.26 (96.45, 100.00)	1.00 (0.38, 1.14)	98.48 (94.64, 100.00)	0.65 (0.02, 1.09)
2D+R (1-12, 1-24)	100.00 (74.30, 100.00)	1.00 (0.39, 1.87)	96.15 (90.93, 100.00)	0.68 (0.02, 2.03)
DCV+SOF (1-12)	100.00 (49.42, 100.00)	1.00 (0.40, 2.11)	--	--
DCV+PR 1-24 or DCV+PR 1-24, PR 25-48	71.01 (60.31, 81.72)	1.34 (0.55, 22.38)	77.78 (50.62, 100.00)	0.70 (0.02, 3.10)

Source: Company submission (tables 46 – 49, pages 137 – 139), ERG report (table 4.17, page 61)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00)

Abbreviations: DCV, daclatasvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; 2D, ombitasvir/paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; RR, relative risk; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response

ERG comments

5.10 The ERG stated that only 29 out of the 40 clinical trials used in the company's network meta-analysis are appropriate for a proper network meta-analysis. The ERG did not believe that combining single arms from studies was a valid and reliable way of synthesising available evidence. It stated that although baseline characteristics appear similar between intervention and comparator trials, the possibility that other factors differed across trials cannot be ruled out. In general, the ERG was concerned about the methodology of both types of evidence synthesis and it considered the outcomes of the analyses to be unreliable. However, the ERG highlighted that a proper network meta-analysis was not possible given the available data presented in the company submission.

Adverse effects of treatment

Clinical trials

5.11 The most commonly reported adverse events in the elbasvir-grazoprevir trials were headache, fatigue, nausea; and the frequency of these adverse events were comparable to the comparator arms, where applicable. Most of the serious adverse events were not considered to be drug-related. There were very few treatment discontinuations due to adverse events across the trials. For the active-controlled trial (C-EDGE H2H), the company stated that the frequency of drug-related adverse events or serious adverse events leading to discontinuation of the study was higher in the sofosbuvir arm than in the elbasvir-grazoprevir arm. Full details of the adverse events are presented on pages 148 – 151 of the company submission.

Network meta-analysis

5.12 The company reported that in general, elbasvir-grazoprevir had a better safety profile across all outcomes (overall adverse event, discontinuation due to adverse events, anaemia, nausea, neutropenia, pruritus and rash) compared to regimens containing peginterferon and/or ribavirin,

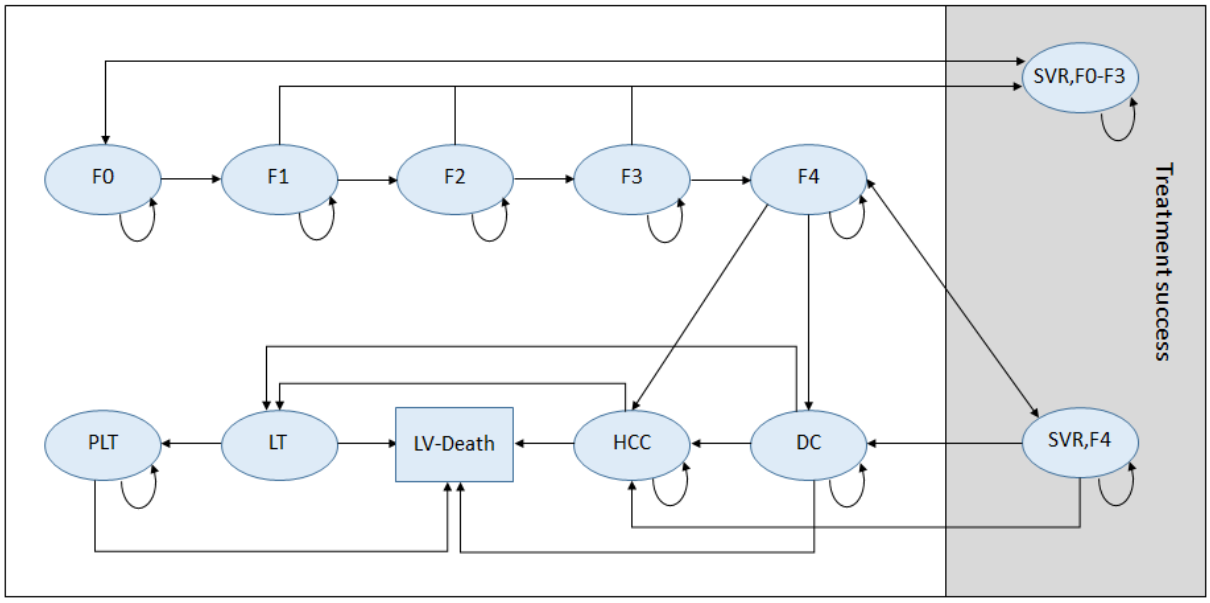
regardless of genotype and cirrhosis status. For most of these outcomes, statistically meaningful differences were observed. When comparing with all-direct acting antivirus (DAA) regimens, only few statistically meaning full differences were observed across the subgroups. Full details of the network meta-analysis safety outcomes are presented on pages 139 – 140 of the company submission.

6 Cost-effectiveness evidence

Model structure

6.1 The company presented a state-transition Markov model to assess the cost-effectiveness of elbasvir-grazoprevir compared with the relevant comparators listed in the company's decision problem (table 4, page 8 of this document) in people with chronic hepatitis C. The model consisted of 13 health states (see figure 1) and is consistent with the models presented for previous NICE appraisals of chronic hepatitis C. Patients are initially distributed equally within the mild (F0-F1) or moderate (F2-F3) health states (no cirrhosis states) or they may enter the model in the cirrhosis health state (F4). The model uses a life-time time horizon up to age 100, with a starting age of 40 or 45 years, in line with recent hepatitis C NICE appraisals. It consists of annual cycle lengths and half cycle correction. Other features of the model are in line with the NICE reference case. The company presented analysis for 12 populations, that is, for genotypes 1a, 1b and 4, and separately by treatment history (treatment naïve and treatment experienced) and cirrhosis status (no cirrhosis and cirrhosis).

Figure 1 Model structure (source: company's response to clarification, page 100)



* The model consists of the following health states: no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), portal fibrosis with numerous septa without cirrhosis (F3), compensated cirrhosis (F4), decompensated cirrhosis (DC) states, hepatocellular carcinoma (HCC) state, two liver transplant states—first year (LT) and subsequent years: post liver transplant (PLT), liver-related death (LV-Death), death from all other causes (not shown here), and two sustained virologic response (SVR) status states stratified by fibrosis stage – 'SVR, F0–F3' and 'SVR, F4'. As shown by the double arrow lines, re-infection can occur from "SVR,F0-F3" to F0 and from "SVR,F4" to F4. The model assumes that patients cannot get re-infected from "SVR,F0-F3" to F1-F3.

ERG comments

6.2 The ERG commented that the model structure was similar to models used in recent hepatitis C NICE appraisals. However, it noted some flaws with the model structure, which includes;

- Health benefits of more effective treatments in preventing future transmissions may have been under-estimated by the model; therefore, a dynamic model would have been more appropriate in order to capture these outcomes.
- The model structure does not allow for subsequent treatments following re-infection.

- The assumption that liver damage due to chronic hepatitis C is fully reversible, that is, patients in the model who become re-infected after achieving an SVR go back to health state F0.

6.3 The ERG stated that the comparators were broadly consistent with the scope, and was satisfied with the exclusion of telaprevir and boceprevir after consulting with their clinical expert. The ERG noted that the company's model does not account for the genotype 1a group, for whom 16 weeks of elbasvir-grazoprevir treatment is recommended in line with the marketing authorisation (see table 1).

6.4 The ERG commented that separate subgroup analyses should have been presented for people with HIV co-infection and people who are intolerant to or ineligible for interferon treatment. It also commented that there could potentially be clinical differences between the different groups of people included in the treatment experienced subpopulation (that is, previous treatment with a DAA versus non-DAA or intolerance to previous treatment versus inadequate response to previous treatment). The ERG noted that further separating the no cirrhosis groups into mild disease (F0-F1) and moderate disease (F2-F3) could have facilitated a comparison of elbasvir-grazoprevir and watchful waiting for the mild disease subgroup.

Model details

6.5 Transition probabilities were used to estimate the proportion of patients in each health state. The base case analysis uses the network meta-analysis results to model SVR, treatment discontinuation rates and adverse events rates for the 5 key drug-related adverse events (anaemia, nausea, neutropenia, rash and pruritus). Genotype 1a or 1b SVR data were used as a proxy for genotype 4 in the company's base case, in line with previous hepatitis C NICE appraisals. The model uses the overall genotype 1 adverse events data for both genotype 1 and 4 subpopulations. Non-treatment specific transition probabilities of moving to more severe health states are taken from different studies, as described on pages 199 – 200 of the company submission.

6.6 In the company's base case, health state utility values and a utility increment of 0.05 for achieving an SVR were derived from published literature (see table 9) in line with previous hepatitis C NICE appraisals. Treatment-specific disutilities were applied to adjust for the impact of adverse events. The model also assumes that health-related quality of life decreases with age.

Table 9 Utility values used in the model (source: ERG report, page 95)

Health states	Mean	SE	Reference
F0 – no fibrosis	0.77	0.02	Wright et al., 2006
F1 – portal fibrosis without septa	0.77	0.02	
F2 – portal fibrosis with few septa	0.66	0.03	
F3 – portal fibrosis with numerous septs without cirrhosis	0.66	0.03	
F4 – compensated cirrhosis	0.55	0.05	
SVR, F0	0.82	0.04	
SVR, F1	0.82	0.04	
SVR, F2	0.71	0.05	
SVR, F3	0.71	0.05	
SVR, F4	0.60	0.06	
DC - Decompensated cirrhosis	0.45	0.045	Ratcliffe et al., 2002[108]
HCC - Hepatocellular carcinoma	0.45	0.045	
LT - Liver transplant (1st year)	0.45	0.045	
PLT - Liver transplant (subsequent years)	0.67	0.067	

6.7 Costs included in the model consisted of drug acquisition costs for elbasvir-grazoprevir and the comparators, monitoring and health state costs and costs associated with managing adverse events. Elbasvir-grazoprevir and some comparators have reduced prices based on contract pricing arrangements between the companies and the Commercial Medicines Unit. However, the company's cost-effectiveness results are based on list prices of all treatments. Details of the resource use and costs are presented on pages 223 – 230 of the company submission.

ERG comments

6.8 The ERG reiterated the limitations with the outcomes from the company's network meta-analysis and naïve indirect comparison, and stated that

cost-effectiveness analyses based on these model inputs should be interpreted with caution. It also considered that defining treatment discontinuation as a result of adverse events only was a limitation in the model.

6.9 The ERG considered the utility data from the elbasvir-grazoprevir trials to be a better reflection of the current UK clinical practice than those from the literature, which were based on data collected many years ago. The ERG also expressed concerns about the company's approach of modelling utility decrements due to adverse events and ageing. The ERG noted that including age-based utility decrements could lead to double-counting. Moreover, these were not included in most of the previous hepatitis C NICE appraisals.

6.10 The ERG did not have any major concerns about the costs and resource use estimates included in the model.

Company's base-case results and sensitivity analysis (list prices)

6.11 The company presented pair-wise incremental cost-effectiveness results (ICERs) for all treatments compared with peginterferon alpha plus ribavirin (PR) because it did not believe that comparing the new direct-acting antivirals (DAAs) based on efficacy was justified given that the network meta-analysis showed no significant differences these treatments. The pair-wise base case, probabilistic sensitivity analyses and deterministic sensitivity analyses results are reported on pages 233 – 237 and 261 – 278 of the company submission. The base case ICERs for elbasvir-grazoprevir compared with PR across the 12 subpopulations were all below £10,000 per QALYs gained.

6.12 The company explored alternative scenarios to address structural and modelling uncertainties. These are reported below for the pair-wise comparison between elbasvir-grazoprevir and PR.

- **SA1:** Using genotype 4-specific data for genotype 4 subpopulation – All but one of the ICERs were below £10,000 per QALY gained (company submission, pages 279 – 282).
- **SA2:** Using data from the naïve comparison rather than the network meta-analysis – ICERs were similar to those using the network meta-analysis data. (company submission, pages 282 – 289).
- **SA3:** Using age-dependent transition probabilities across fibrosis health states F0-F3 from Grishchenko et al. 2009 rather than Thein et al. 2008 – ICERs ranged from £6,418 to £23,347 per QALY gained (company submission, pages 289 – 294).
- **SA4:** Using data for European patients from the trials rather than Wright et al. 2006 to derive utility increment from achieving SVR – slight increase in the ICERs, with the highest ICER approximately £10,500 per QALY gained (company submission, pages 294 – 298).
- **SA5:** Assuming a probability of regression from SVR F4 to SVR F0-F3 based on D'Ambrosio et al. 2012 (0.167) – ICERs for cirrhosis groups decrease significantly (company submission, pages 298 – 302).
- **SA6:** Using a 5-year and 10-year time horizons – ICERs were above £30,000 per QALY gained, the magnitude of the increase was greater with a 5-year horizon (company submission, pages 302 – 310).

6.13 The company also presented fully incremental results in Appendix 22 of the company submission. For all the subpopulations without cirrhosis, elbasvir-grazoprevir was dominated. For the subpopulations with cirrhosis, the ICERs for elbasvir-grazoprevir compared with the next non-dominated alternative for the genotype 1b groups were above £30,000 per QALY gained, whereas those for genotypes 1a and 4 ranged from £6,396 to £21,343 per QALY gained. These results should be interpreted with caution given that there were marginal differences in QALYs across all treatments; which mean that small differences in costs had a dramatic effect on the results.

ERG exploratory analyses

6.14 The ERG revised the company's base case using the following preferred assumptions;

- Adjusting the model structure so that patients who become re-infected after achieving an SVR return to their pre-SVR fibrosis health state
- Using SVR-related utility increments derived from the European subgroup of the elbasvir-grazoprevir trials
- Excluding age-based utility decrements from the base case

The list price ICERs for elbasvir-grazoprevir compared with PR for the no cirrhosis subpopulations increased by approximately £3,000 per QALY gained, whereas the ICERs for the cirrhosis subpopulations were similar to the company's base case ICERs.

6.15 When the confidential price reductions for elbasvir- grazoprevir, 3D/2D and daclatasvir were applied in the company's base case and the ERG's revised base case, [redacted]

6.16 The ERG conducted 7 scenario analyses. Scenarios 1-3 are similar to the company's scenarios 1-3. Scenarios 4, 6 and 7 used the company's base case assumptions of patients returning to health state F0 after reinfection, SVR-related utility increment of 0.05 from Wright et al. 2006 and applying age-based utility decrements respectively. For scenario 5, the ERG applied uniform disutilities from adverse events to the all-DAA treatments. With the exception of scenario 3, the scenario analyses had little or moderate impact on the ICERs for elbasvir-grazoprevir.

6.17 When the confidential price reductions were applied in the ERG's scenario analyses, [redacted] for all scenarios except for scenario 3 (genotype 1a no cirrhosis groups only) and scenario 1 (genotype 4, treatment experienced with cirrhosis). When genotype 4

specific data was used in scenario 1 for the genotype 4, treatment experienced with cirrhosis subpopulation, the full incremental analysis showed that [redacted].

Innovation

6.18 Justifications for considering elbasvir-grazoprevir to be innovative:

- The company stated that there is significant unmet need in people with chronic hepatitis C complicated by severe renal disease. The product label of elbasvir-grazoprevir does not require dose adjustment with regard to any degree of renal impairment compared.

7 Equality issues

7.1 The company and professional organisations raised some equality issues that have been discussed in previous chronic hepatitis C NICE appraisals such as higher prevalence of disease or specific genotypes (genotype 4) in people who inject drugs and among minority ethnic groups. In previous appraisals, the committee had attempted to bridge the evidence gap for genotype 4 by accepting genotype 1 data as a proxy for genotype 4. In addition, the company also stated that there is stigma associated with people who have hepatitis C and chronic kidney disease because they are made to receive dialysis treatment in a separate 'special' room. Also people with HIV co-infection are more likely to disclose their HIV status than their hepatitis C status because of the perceived stigma around hepatitis C due to lack of hepatitis C awareness.

8 Authors

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Grazoprevir–elbasvir for treating chronic hepatitis C

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of grazoprevir–elbasvir within its marketing authorisation for treating chronic hepatitis C.

Background

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

Chronic hepatitis C is categorised according to the extent of liver damage, as mild, moderate, or severe (where severe refers to cirrhosis). About 20% of people with chronic hepatitis C will develop cirrhosis[2]; the time for progression to cirrhosis varies, but takes 20-30 years on average[2]. Cirrhosis can progress to become 'decompensated', where the remaining liver can no longer compensate for the loss of function. A small percentage of people with chronic hepatitis and cirrhosis also develop hepatocellular carcinoma. Liver transplantation may be needed for people with decompensated cirrhosis or hepatocellular carcinoma.

The true prevalence of HCV infection is difficult to establish and likely to be underestimated because many people do not have symptoms. As a result a significant number of people remain undiagnosed. There are 6 major genotypes and several subtypes of HCV; the prevalence of each varies geographically. Recent estimates (2012) suggest that around 160,000 people are chronically infected with HCV in England[4], and that approximately 90% of these people are infected with genotype 1 or genotype 3[4].

The aim of treatment is to cure the HCV infection, and prevent liver disease progression, hepatocellular carcinoma development, and HCV transmission. The HCV genotype influences treatment decisions and response. For those with mild hepatitis C, a 'watchful waiting' approach may be agreed between the patient and clinician on an individual basis. NICE guidance on hepatitis C (NICE technology appraisal guidance 75, 106, 200, 252, 253, 330, 331, 363, 364 and 365) recommend:

- combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b for people with chronic hepatitis C regardless of disease severity, genotype or treatment experience.

- monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended for people who are unable to tolerate ribavirin or for whom ribavirin is contraindicated.

- telaprevir in combination with peginterferon alfa and ribavirin for people with genotype 1 chronic hepatitis C.

- boceprevir in combination with peginterferon alfa and ribavirin for people with genotype 1 chronic hepatitis C.

- sofosbuvir in combination with ribavirin, with or without peginterferon alfa, as an option for specific people with genotypes 1–6 chronic hepatitis C.

- simeprevir in combination with peginterferon alfa and ribavirin as an option for people with genotype 1 or 4 chronic hepatitis C

- ledipasvir–sofosbuvir as an option for specific people with genotype 1 or 4 chronic hepatitis C

- daclatasvir in combination with sofosbuvir, with or without ribavirin, as an option for specific people with genotype 1, 3 or 4 chronic hepatitis C

- daclatasvir in combination with peginterferon alfa and ribavirin, as an option for specific people with genotype 4 chronic hepatitis C

- ombitasvir–paritaprevir–ritonavir with or without dasabuvir or ribavirin as an option for genotype 1 or 4 chronic hepatitis C.

The technology

Grazoprevir–elbasvir (brand name unknown, Merck Sharp & Dohme) disrupts the biogenesis of components necessary for HCV replication by inhibiting key HCV proteins. It is orally administered as a fixed-dose combination product.

Grazoprevir–elbasvir does not currently have a marketing authorisation in the UK for treating chronic hepatitis C. It has been studied in clinical trials as monotherapy and in combination with ribavirin or sofosbuvir in adults with genotype 1–6 HCV.

Intervention(s)	Grazoprevir–elbasvir

Population(s)	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)
Comparators	• best supportive care (watchful waiting) (genotypes 1-6) • boceprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only) • daclatasvir in combination with peginterferon alfa and ribavirin (for specific people with genotype 4; as recommended by NICE) • daclatasvir in combination with sofosbuvir, with or without ribavirin (for specific people with genotype 1, 3 or 4; as recommended by NICE) • ledipasvir–sofosbuvir (for specific people with genotype 1 or 4; as recommended by NICE) • ombitasvir–paritaprevir–ritonavir with or without dasabuvir or ribavirin (for genotype 1 or 4) • peginterferon alfa with ribavirin (for genotypes 1-6) • simeprevir in combination with peginterferon alfa and ribavirin (for genotype 1 or 4) • sofosbuvir in combination with ribavirin, with or without peginterferon alfa (for specific people with genotypes 1-6; as recommended by NICE) • telaprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only)
Outcomes	The outcome measures to be considered include: • sustained virological response • development of resistance to grazoprevir–elbasvir • mortality • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If evidence allows the following subgroups will be considered: • genotype • people with renal impairment • co-infection with HIV • people with and without cirrhosis • people with advanced liver disease • post-liver transplantation • people with haemoglobinopathies (for example, sickle cell disease, thalassaemia major) • response to previous treatment (non-response, partial response, relapsed) • people who are intolerant to or ineligible for interferon treatment If evidence allows the impact of treatment on reduced onward HCV transmission will also be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C' (2015). NICE Technology Appraisal 365. 'Daclatasvir for treating chronic hepatitis C' (2015). NICE Technology Appraisal 364. 'Ledipasvir–sofosbuvir for treating chronic hepatitis C'

	(2015). NICE Technology Appraisal 363. 'Simeprevir for treating genotype 1 or 4 chronic hepatitis C' (2015). NICE Technology Appraisal 331. Review date February 2016. 'Sofosbuvir for treating chronic hepatitis C' (2015). NICE Technology Appraisal 330. Review date February 2016. 'Boceprevir for the treatment of genotype 1 chronic hepatitis C' (2012). NICE Technology Appraisal 253. Review Date April 2015. 'Telaprevir for the treatment of genotype 1 chronic hepatitis C' (2012). NICE Technology Appraisal 252. Review Date April 2015. 'Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C' (2010). NICE Technology Appraisal 200. Guidance added to static list December 2013. 'Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C (partially updated in TA200)' (2006). NICE Technology Appraisal 106. Guidance added to static list December 2013. 'Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C (partially updated in TA200)' (2004). NICE Technology Appraisal 75. Guidance added to static list December 2013. Related Guidelines: 'Hepatitis C: Diagnosis and management of hepatitis C'. NICE Clinical Guideline. Publication date to be confirmed. Related Public Health Guidance: 'Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection' (2012). NICE Public Health Guidance 43. Related NICE Pathways: 'Hepatitis B and C' (2012). NICE pathway. http://pathways.nice.org.uk/pathways/hepatitis-b-and-c-testing

Related National Policy	Clinical Commissioning Policy Statement: Treatment of chronic Hepatitis C in patients with cirrhosis: http://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/06/hep-c-cirrhosis-polcy-statmnt-0615.pdf NHS England Manual for prescribed specialised services 2013/2014. Sections 16 and 65: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 2–4. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

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Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

Matrix of consultees and commentators

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

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

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

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

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

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

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

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

Commentators

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

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Elbasvir-grazoprevir for treating chronic hepatitis C [ID842]
Merck Sharp & Dohme: Evidence submission

22nd April 2016

File name	Version	Contains confidential information	Date
		Yes	

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Abbreviations

Abbreviation	Definition
2D	Ombitasvir–paritaprevir–ritonavir
3D	Ombitasvir–paritaprevir–ritonavir with dasabuvir
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
APaT	All patients as treated
ART	Antiretroviral treatment
BASL	British Association for the Study of Liver
BHIVA	British HIV Association
BOC	Boceprevir
C	Cirrhotic
CADTH	Canadian Agency for Drugs and Technologies in Health
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 Review and Dissemination
CrI	Credible interval
CSR	Clinical study report
CUA	Cost utility analysis
DAA	Direct-acting antivirals
DAE	Discontinuation due to adverse events
DAO	Data as observed approach
DCV	Daclatasvir
DoH	Department of Health
EASL	European Association for the Study of Liver
ECG	Electrocardiogram
EMA	European Medicine Agency
eRVR	Extended rapid viral response
EQ-5D-3L	EuroQol-5 Dimension 3-Level
EQ-5D-3L	EuroQol-5 Dimension 5-Level
ESRD	End stage renal disease
EVR	Early viral response
FAS	Full analysis set
FDA	Food and Drug Administration
GT	Genotype
EBR/GZR	Grazoprevir/elbasvir
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV/HIV-1	Human immunodeficiency virus
HRQoL	Health related Quality of life

Abbreviation	Definition
ICER	Incremental cost effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IFN	Interferon
ISPOR	International Society for Pharmacoecomics and Outcomes Research
ITT	Intention to treat
IU	International unit
KOL	Key opinion leader
LDV	Ledipasvir
LLoQ	lower limit of quantification
M=F	Missing = Failure
MCMC	Markov Chain Monte Carlo
MDT	Multi-disciplinary teams
mFAS	Modified full analysis set
mITT	Modified intention to treat
MSD	Merck Sharp and Dohme
NA	Not applicable
NC	Non-cirrhotic
NHSE	National health service England
NHS	National health service
NHS-EED	National health services-Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not reported
NS5A	Non-structural protein 5A
OAE	Overall adverse events
OATP	Organic anion transporting polypeptide
OB	Observed failure
ODN	Operational delivery networks
OST	Opiate substitution therapy
OVID	Data base search platform for SLR
PCR	Polymerase chain reaction
PEG-IFN alpha	Pegylated-interferon alpha
PHE	Public health England
PICOS	Patient, Interventions, Comparators, Outcomes, Stud design
PP	Per protocol
PR	Pegylated-interferon alpha/RBV
PRO	Patient Reported Outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PWIDs	People who inject drugs
QALY	Quality adjusted life year
QoL	Quality of life
RAVs	Resistance-associated variants
RBV	Ribavirin
RCGP	Royal College of General Practitioners
RCT	Randomised control trial

Abbreviation	Definition
RNA	Ribonucleic acid
SIGN	Scottish Intercollegiate Guidelines Network's
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMV	Simeprevir
SOF	Sofosbuvir
LDV/SOF	Harvoni (Sofosbuvir/Ledipasvir)
SVR	Sustained virologic response
TA	Technology appraisal
TBC	To Be Confirmed
TD	Target detected
Tdu	Target detected unquantifiable
TE	Treatment-experienced
TN	Treatment-naïve
TND	Target not detected
TRD= F	Treatment discontinuation = failure.
TVR	Telaprevir
VIRS	Voice interactive response system
WHO	World Health Organization
WTP	Willingness to pay

1 Executive summary

Brief background to the condition

Hepatitis C virus (HCV) is a blood-borne, ribonucleic acid (RNA), virus that primarily affects the liver (hepatocytes), but can also be found in the bone marrow, central nervous system, endocrine glands, lymphatic tissue, and skin cells[1]. Chronic hepatitis C (CHC) occurs in up to 80% of infected individuals, although the acute infection may resolve [2]. Chronic hepatitis is characterised by degrees of liver inflammation and stages of fibrosis. The manifestation of symptoms in patients infected with chronic HCV may take up to 30 years, thus a large proportion of those infected remain unaware of their status. This can lead to onward transmission (incidence), progression to cirrhosis and/or liver decompensation, which may necessitate a liver transplant; all of which carry substantial resource implications for both public health, and the NHS. A small percentage of people (i.e. ~2-4%)[3] with CHC and cirrhosis also develop hepatocellular carcinoma (HCC), a significant cause of morbidity, mortality, and cost. Individuals infected with HCV are at an increased risk of developing chronic kidney disease (CKD) and end stage renal disease (ESRD) compared with patients who are not infected with HCV[4, 5]. Furthermore, HCV infection can have physical and emotional consequences for the patients, negatively impacting their quality of life (QoL). Fatigue and depression are common in these patients with lower mental and physical component summary scores compared with uninfected individuals[6, 7].

In the UK, ~214,000 individuals are thought to be chronically infected with HCV, of which ~160,000 people are in England alone[8]. In the UK, genotypes (GT) 1 and 3 are equally distributed accounting for 90% of infections, GT2 for 6%, GT4 for 4%, and GT5 and GT6 for less than 1%[9] .

The primary goal of current HCV therapy is treatment cure in order to prevent premature morbidity and mortality. In addition, treatment cure has the ability to reduce the rates of transmission and the prevalence of HCV in the general population. Treatment cure is assessed using sustained virologic response (SVR); this is defined as an undetectable HCV RNA at 12 weeks (SVR12) or 24 weeks (SVR24) after the completion of HCV treatment. The HCV infection is cured in >99% of patients who achieve a SVR; and thus, associated with disease resolution in patients without cirrhosis.

The approval of the second-generation direct-acting antivirals (DAAs) has changed the HCV treatment landscape considerably. These treatment regimens offer an all-oral route of administration, higher levels of efficacy (SVR12 above 90%), and a favourable

safety/tolerability profile compared with historic PR regimens. This is supported by recent guidance, which supports DAA use as current clinical practice (see section 3.6).

Successful HCV treatment can lead to an overall risk reduction in: liver and non-liver related mortality, the development of HCC, and medical resource costs. Treatment can also lead to an improved QoL for patients, positively affecting their capacity for leisure and work activity. HCV treatment initiated earlier in the disease pathway leads to: greater and more rapid improvements in morbidity, a reduced risk of transmission, and HCV-related mortality.

Elbasvir/grazoprevir EBR/GZR is a single fixed dose combination (FDC) oral tablet taken once daily for 12 weeks (see Appendix 1). This submission considers EBR/GZR for use in patients diagnosed with HCV GT1a, GT1b, or GT4 infections, irrespective of treatment experience or cirrhosis stage. Therefore, EBR/GZR is expected to displace a level of use for those technologies, previously recommended by NICE, relevant to the GT (subtypes) considered within this submission

The efficacy (SVR12) and safety/tolerability of EBR/GZR has been evaluated in eight clinical trials. This consists of five phase III, one phase II/III, and two phase II trials, in which patients were randomised (n=7 trials) to receive EBR/GZR for 12 weeks. The inclusion of these trials represents a diverse patient population, including: CKD stages 4-5, HIV co-infection, prior PR treatment failure, opiate substitution therapy (OST), and treatment naïve cirrhotic/non-cirrhotic patients, all of which are eligible for treatment in UK clinical practice.

The pooled SVR12 results demonstrate that EBR/GZR is a highly efficacious treatment option for all patient groups, irrespective of treatment experience or cirrhosis state: GT1a (range 91-97%), GT1b (range 98-100%), and GT4 (range 67-100%) infections. The NMA revealed no statistically significant differences between the SVRs achieved with EBR/GZR and the other all-DAA regimens (LDV/SOF, OMB+PAR/r±DAS±RBV, and DCV+SOF) in any of the subgroups that were investigated. The results of the naïve comparison and NMA were broadly consistent, especially for the all-DAA regimens.

A Markov model, consisting of 13 health states, reflecting the natural history of HCV, was developed to assess the cost-effectiveness of EBR/GZR vs. relevant comparators. The model structure reflects published HCV models in the UK and is broadly comparable with those previously submitted to NICE. The model takes into account the main efficacy outcome (SVR12), and commonly reported AEs reported in the EBR/GZR and comparator trials. Based on the short duration of treatment associated with the DAA regimens, the model considered all treatment related-outcomes within the first year.

The results are consistent across the base case scenario and the PSA. EBR/GZR is a cost-effective option for the treatment of patients with HCV GT1a, GT1b, and GT4 infections. The

base case ICER for EBR/GZR compared to PR, based on list prices, was below £10,000 across all subgroups

All of the results presented, for EBR/GZR and relevant comparators were based on list price (given the lack of information publicly available on comparators CMU prices, when applicable). Therefore, MSD is not able to accurately capture the cost-effectiveness of EBR/GZR or the recently approved DAAs. The results should therefore be considered indicative and not reflective of the current HCV commercial landscape.

Given the constrained NHSE budget and the affordability issues associated with the DAA treatment regimens, MSD has agreed a price with the commercial medicines unit (CMU). Therefore, EBR/GZR will not have any additional budget impact.

MSD has demonstrated, based on comparative clinical and cost-effective data, that EBR/GZR is a highly effective and cost-effective treatment option for patients with chronic HCV GT1 and GT4 infections.

1.1 Statement of decision problem

Table 1. The decision problem

	Final scope issued by NICE (February 2016)	Original decision problem (February 2016)	New decision problem that will be addressed in the company submission* (April 2016)	Changes
Population	People with chronic hepatitis C: • Who have not had treatment for chronic hepatitis C (CHC) (treatment-naïve) • Who have had treatment for chronic hepatitis C (treatment-experienced)	People with chronic hepatitis C: • Who have not had treatment for chronic hepatitis C (CHC) (treatment-naïve) • Who have had treatment for chronic hepatitis C (treatment-experienced)	People with chronic hepatitis C: • Who have not had treatment for chronic hepatitis C (treatment-naïve) • Who have had treatment for chronic hepatitis C (treatment-experienced)	As specified in the scope, however please note that the anticipated product label does not differentiate between treatment-naïve/treatment-experience, cirrhotic/non-cirrhotic HCV patients.
Intervention	Grazoprevir-elbasvir	Grazoprevir-elbasvir with or without ribavirin	Elbasvir/grazoprevir for 12 weeks	As specified in the scope in line with the anticipated product label.
Comparator (s)	• best supportive care (watchful waiting) (GT1-6) • boceprevir in combination with peginterferon alfa and ribavirin (for GT1 only) • daclatasvir in combination with peginterferon alfa and ribavirin (for specific people with GT4; as recommended by NICE) • daclatasvir in combination with sofosbuvir, with or without ribavirin (for specific people with GT1, 3 or 4; as recommended by NICE) • ledipasvir–sofosbuvir (for specific people with GT1 or 4; as recommended by NICE) • ombitasvir–paritaprevir–ritonavir with or without dasabuvir or	• best supportive care (watchful waiting) (GT1 and GT4) (potentially GT3) • daclatasvir in combination with ribavirin, with or without peginterferon alfa (GT4) • daclatasvir in combination with sofosbuvir, with or without ribavirin (GT1 and GT4) (Potentially GT3) • ledipasvir–sofosbuvir with or without ribavirin (GT1 and GT4) • ombitasvir/paritaprevir/ritonavir with or without dasabuvir (GT1 and GT4) • peginterferon alfa with ribavirin (GT1 and GT4, potentially GT3)	• best supportive care (watchful waiting) (GT1 and GT4) • daclatasvir in combination with ribavirin, with or without peginterferon alfa (GT4) • daclatasvir in combination with sofosbuvir, with or without ribavirin (GT1 and GT4) • ledipasvir–sofosbuvir with or without ribavirin (GT1 and GT4) • ombitasvir/paritaprevir/ritonavir with or without dasabuvir (GT1 and GT4) • peginterferon alfa with ribavirin (GT1 and GT4) • simeprevir in combination with peginterferon alfa and ribavirin	As specified in the scope, but adapted to be more specific with the product label. "Best supportive care" is defined as no treatment. As per the clarification comments provided by MSD on the draft scope for EBR/GZR, MSD does not believe that it is appropriate to include boceprevir and telaprevir within the decision problem. The rationale for this includes: treatment regimens are no longer representative of current clinical practice following the introduction and approval of the newer DAA technologies (TA330, TA363, TA364, and TA365), [10-13] [redacted] When the data allowed, MSD performed comparison in line with the license for EBR/GZR with the comparator agents listed in

	Final scope issued by NICE (February 2016)	Original decision problem (February 2016)	New decision problem that will be addressed in the company submission* (April 2016)	Changes
	ribavirin (for GT1 or 4) • peginterferon alfa with ribavirin (for GT1-6) • simeprevir in combination with peginterferon alfa and ribavirin (for GT1 or 4) • sofosbuvir in combination with ribavirin, with or without peginterferon alfa (for specific people with GT1-6; as recommended by NICE) • telaprevir in combination with peginterferon alfa and ribavirin (for GT1 only)		(GT1 and GT4) • sofosbuvir in combination with ribavirin, with or without peginterferon alfa (for specific people with GT1 and GT4, potentially 3; as recommended by NICE)	the final scope. Assumptions were made when evidence did not allow comparison.
Outcomes	The outcome measures to be considered include: • sustained virological response • development of resistance to grazoprevir–elbasvir • mortality • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • sustained virological response • development of resistance to grazoprevir–elbasvir • mortality • adverse effects of treatment health-related quality of life.	The outcome measures to be considered include: • sustained virological response • mortality • adverse effects of treatment • health-related quality of life.	In line with NICE final scope. RAVS was not considered in post hoc analyses and therefore do not support the economic analyses.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to	In line with the final scope.

	Final scope issued by NICE (February 2016)	Original decision problem (February 2016)	New decision problem that will be addressed in the company submission* (April 2016)	Changes
	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	
Subgroups to be considered	If evidence allows the following subgroups will be considered: • genotype • people with renal impairment • co-infection with HIV • people with and without cirrhosis • people with advanced liver disease • post-liver transplantation • people with haemoglobinopathies (for example, sickle cell disease, thalassaemia major) • response to previous treatment (non-response, partial response, relapsed) • people who are intolerant to or ineligible for interferon treatment	When evidence allows the following subgroups are considered: <u>Health economic analysis</u> • Genotype • Co-infection with HIV ○ MSD would suggest that this is not a subgroup of interest for this decision problem. ○ SVR rates are comparable across HIV co-infected and non-HIV infected patients. ○ Clinical opinion has confirmed that HIV does not represent a discrete patient group, and that HIV co-infected patients should be considered as part of the whole HCV population. • People with and without cirrhosis • Post-liver transplantation ○ MSD previously highlighted that a post-liver transplant population would not be included within the grazoprevir/elbasvir license. ○ MSD is not aware of any	Analyses are provided on the following subgroups: • genotype • people with and without cirrhosis • response to previous treatment (non-response, partial response, relapsed)	MSD will not be considering the following subgroups as no different treatment regimen is indicated for our product label: • people with renal impairment. Although one of the EBR/GZR clinical trials included CKD patients (i.e. C-SURFER),[14] there is a lack of data in CKD patients overall as no other clinical trials are known in this population; thus preventing comparisons. In addition, our clinical trial results suggest that SVR rates in this specific group is comparable to other EBR/GZR trials. • people co-infected with HIV. As per EASL 2015 guidelines: patients should receive the same treatment duration and regimen as those who are HCV mono-infected.[15] Furthermore, IFN-free regimens report identical virological results. As per the EBR/GZR trials SVRs were comparable. • people with advanced liver disease. There is paucity of data in this subgroup for EBR/GZR and comparator agents. This subgroup was not examined in previous submissions. • post-liver transplantation. MSD had previously indicated at the draft scope stage that a post-liver transplant population would not be included within the EBR/GZR license. MSD is not aware of any specific data for

	Final scope issued by NICE (February 2016)	Original decision problem (February 2016)	New decision problem that will be addressed in the company submission* (April 2016)	Changes
		specific data for grazoprevir/elbasvir in patients post liver transplant • People with haemoglobinopathies (for example, sickle cell disease, thalassaemia major) ○ MSD had previously indicated at the draft scope stage that data may be available in this specific subgroup. ○ The specific inherited blood disorders study is not expected to be available in CSR form until Q3 2016 (C-EDGE inherited blood disorders). ○ This subgroup has not been considered in previous HCV submissions. MSD believes that this patient group would experience comparable SVR rates and therefore would be included within the overall population. Furthermore, due to a lack of comparative data with previous HCV submissions it would be difficult to draw any strong conclusions. • Response to previous treatment (non-response, partial response, relapsed) ○ MSD will have to make assumption regarding the terminology OTVF relative to NICE approved comparators. This is discussed further in		EBR/GZR in patients post liver transplant. • people with haemoglobinopathies (for example, sickle cell disease, thalassemia major). MSD had previously indicated at the draft scope stage that data may be available in this subgroup, however, the specific inherited blood disorders study is not expected to be available in CSR form until [redacted] (C-EDGE inherited blood disorders). • people who are intolerant to or ineligible for IFN treatment. EBR/GZR is an IFN-free regimen.

	Final scope issued by NICE (February 2016)	Original decision problem (February 2016)	New decision problem that will be addressed in the company submission* (April 2016)	Changes
		section 4 below. • People who are intolerant to or ineligible for interferon treatment • If evidence allows the impact of treatment on reduced onward HCV transmission will also be considered. MSD accepts that NICE guidance will only be issued in accordance with the marketing authorisation, once confirmed. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		
Special considerations including issues related to equity or equality	None stated	None stated	None stated	In line with the final scope.

Abbreviations. CHC, chronic hepatitis C; CKD, chronic kidney disease; EASL, European association for the study of liver; EBR/GZR, grazoprevir/elbasvir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTA, health technology assessment; SVR, sustained virological response; TA, technology appraisal.
Notes: *based on the draft SmPC received at day 180

1.2 Description of the technology being appraised

The technology being appraised (EBR/GZR) is described in Table 2 below:

Table 2. Technology being appraised

UK approved name and brand name	ZEPATIER® (elbasvir/grazoprevir)
Marketing authorisation/CE mark status	It is anticipated that the Committee for Medicinal Products for Human Use (CHMP) will issue a positive opinion on ZEPATIER for the treatment of CHC in May 2016. Marketing authorisation is expected in August 2016.
Indications and any restriction(s) as described in the summary of product characteristics	Indication to which this submission relates: ZEPATIER is indicated for the treatment of CHC in adults.
Method of administration and dosage	Oral. EBR 50mg and GZR 100mg, as a single fixed-dose combination tablet administered once daily. It can be taken with or without food.

EBR/GZR combines two DAA agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. Grazoprevir is an inhibitor of the HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. EBR/GZR is a FDC single tablet containing 50mg of elbasvir and 100 mg of grazoprevir for oral administration once daily without regard for food.

EBR/GZR is currently under review by the European Medicines Agency (EMA) via the centralised procedure. MSD anticipates the marketing authorisation in August 2016, following a positive CHMP opinion on the 26th of May 2016. The license indication will be for the treatment of CHC in adults infected with HCV GT1a, GT1b, and GT4 irrespective of treatment experience and cirrhosis stage.

According to new guidelines DAAs now constitute routine clinical practice (see section 3.6). EBR/GZR represents an IFN and RBV-free DAA regimen with a treatment duration of 12 weeks for patients with HCV GT1a, GT1b, and GT4 infections. The treatment duration may be increased to 16 weeks in combination with ribavirin at the discretion of physicians (see appendix 1).

The list price of EBR/GZR for a 28-day pack is £12,166.67 (the maximum price payable within NHS Framework Agreements between MSD and CMU for a 28-day pack is [redacted],

the maximum price payable per patient based on the same agreement [redacted]).

1.3 Summary of the clinical effectiveness analysis

The efficacy (SVR12) and safety/tolerability of EBR/GZR has been evaluated in eight clinical trials as described in this submission. This consists of five phase III, one phase II/III, and two phase II trials, in which patients were randomised (n=7 trials) to receive EBR/GZR for 12 weeks. The inclusion of these trials represents a diverse patient population; CKD stages 4-5, HIV co-infected, prior PR treatment failures, opiate substitution therapy (OST), and treatment naïve cirrhotic/non-cirrhotic patients, all of which are eligible for treatment in UK clinical practice.

To enable a meaningful comparison of efficacy of NICE recommended treatment regimens, post hoc-analysis of the included EBR/GZR CSRs was conducted. From each CSR EBR/GZR 12 weeks was split according to treatment experience and cirrhotic status for patients with HCV GT1a, GT1b, or GT4 infections. These post-hoc analysis data were then used to inform the NMA and subsequent health economic analyses. In addition, assumptions were also made to allow for comparisons of interventions were data were not available or considered to be not robust, i.e. the use of GT1 overall data split by cirrhotic/non-cirrhotic status when sub-GT data were not available, the use of GT1 as a proxy for GT4, and the use of GT1 overall as a proxy for GT1a or GT1b.

The pooled SVR12 results demonstrate that EBR/GZR is a highly efficacious treatment option for all patients groups, irrespective of treatment experience or cirrhosis state: GT1a (range 91-97%), GT1b (range 98-100%), and GT4 (range 67-100%) infections. Note that the lower estimate of SVR12 reported in GT4 was based on 6 patients described as GT4 treatment experienced cirrhotic (SVR12, 66.67%) and represents the general paucity of data for this patient subgroup.

The NMA revealed no significant differences between SVRs with EBR/GZR and the other all-DAA regimens (LDV/SOF, OMB+PAR/r±DAS±RBV, and DCV+SOF) in any of the subgroups that were investigated. The results of the naïve comparison and NMA were broadly consistent, especially for the all-DAA regimens.

Clinical data demonstrate that EBR/GZR has a favourable safety and tolerability profile when compared with placebo or active control (SOF+PR) for the treatment of patients with HCV GT1 and GT4 infections, irrespective of cirrhosis stage or treatment experience. Across the trial populations (described above), the most commonly reported adverse events (AEs) included fatigue, headache, nausea, and in some cases diarrhoea, dizziness, and cough.

Discontinuation related to drug related AE/SAE were rare, and there was no mortality associated with the use EBR/GZR. Using post-hoc analysis data a NMA of safety for EBR/GZR 12 weeks was conducted. Due to a paucity of data for the interventions of interest the following assumptions were made: GT1 overall was used as a proxy for GT1a and GT1b, GT1 data would be used as a proxy for GT4 data when unavailable for the safety analysis. GT1 and GT4 data were split according to cirrhosis state only, as this was considered a key prognostic factor. The results show generally lower rates of AE for EBR/GZR compared with regimens containing Peg IFN and/or RBV in patients with GT1, regardless of cirrhosis status; and for GT4, fewer meaningful differences were observed.

The evidence presented supports the use of EBR/GZR in patient groups considered difficult to treat (prior treatment failures), those who are co-infected with HIV and HCV, and in those who are considered to have high unmet clinical need (CKD, stage 4-5). Furthermore, EBR/GZR was shown to be highly efficacious and safe in the treatment of patients in receipt of OST, thought to represent a significant number of patients in the UK.

1.4 Summary of the cost-effectiveness analysis

A Markov model, consisting of 13 health states and reflecting the natural history of HCV, was developed to assess the cost-effectiveness of EBR/GZR vs. relevant comparators. The model structure reflects published HCV models in the UK and is broadly comparable with those previously submitted to NICE. The model takes into account the main efficacy outcome, SVR12 and commonly reported AEs, as reported in the EBR/GZR and comparator trials. Based on the short duration of treatment associated with DAA regimens, the model considered all treatment related-outcomes within the first year.

Patients enter the model in either the non-cirrhotic or cirrhotic health states. Patients who respond to antiviral therapy (achieve SVR) enter the SVR health state, which is conditioned to their baseline fibrosis stage at treatment initiation allowing for the possibility of differences in risk and outcomes (i.e. previously cirrhotic patients are assumed to have an excess risk of DC and HCC). Patients who achieve SVR are also assumed to face a small, but constant, risk of re-infection; this assumed they continue to expose themselves to the risk of HCV infection.

Patients who are treated unsuccessfully, and fail to achieve SVR may experience: liver disease progression, and relevant complications such as DC, HCC liver failure requiring liver transplant.

The model projected health outcomes (i.e. SVR) to estimate patients' health-related quality of life (HRQoL) and costs. Quality-adjusted life years (QALYs) were taken from the

published literature and adjusted with specific EBR/GZR trial data. Clinical and economic outcomes were projected over a lifetime horizon to cover the anticipated lifetime of the target population initiating HCV treatments.

Using the results of the NMA, pairwise comparisons using PR as a comparator vs. EBR/GZR and other regimens was undertaken; these analyses were split according to cirrhotic and non-cirrhotic subpopulations as per the NICE final scope. Given the limited number of GT4 HCV patients in EBR/GZR clinical trials, in line with KOLs' feedback and with previous HCV models submitted to NICE, GT1 data is used as a proxy for GT4 in the base case scenario. GT4 data is tested in scenario analysis.

Section 5 details the development of the de novo economic model for EBR/GZR, with Table 3 to Table 14 below presenting the base case results for each subpopulation.

It should be noted that all the results are based on list price; this is for EBR/GZR and all comparators (given the lack of information publicly available on comparators CMU prices, when applicable). Therefore, MSD is not able to accurately capture the cost-effectiveness of EBR/GZR or the recently approved DAAs. The results should therefore be considered indicative and not reflective of the current HCV commercial landscape.

The results are consistent across the base case scenario and the PSA. EBR/GZR is a cost-effective option for the treatment of patients with HCV GT1a, GT1b and GT4 infections. In the base case, the ICER for EBR/GZR compared to PR, based on list prices is below £10K across all subgroups.

Table 3. Base case results – GT1a TN C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,599	15.526	7.741	-	-	-	-
SOF	£64,907	16.928	8.845	£10,308	1.402	1.104	£9,338
SMV	£65,380	16.384	8.456	£10,781	0.858	0.714	£15,095
EBR/GZR	£68,555	17.498	9.260	£13,956	1.973	1.518	£9,193
LDV/SOF	£70,941	17.498	9.259	£16,342	1.972	1.518	£10,765
2D/3D	£96,765	17.435	9.208	£42,166	1.909	1.467	£28,742

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 4. Base case results – GT1a TN NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,580	20.781	13.473	-	-	-	-
BSC	£30,513	19.183	11.404	£3,932	-1.598	-2.069	Dominated
LDV/SOF	£32,059	21.663	15.098	£5,479	0.882	1.625	£3,371
SMV	£36,693	21.360	14.550	£10,113	0.579	1.077	£9,388
2D/3D	£40,479	21.757	15.225	£13,899	0.976	1.752	£7,935
EBR/GZR	£42,389	21.707	15.150	£15,809	0.926	1.677	£9,427
SOF	£43,855	21.590	14.942	£17,275	0.809	1.469	£11,762
DCV+SOF	£64,902	21.757	15.217	£38,321	0.976	1.744	£21,976

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 5. Base case results – GT1a TE C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£55,175	14.627	7.447	-	-	-	-
SMV	£61,679	16.035	8.592	£6,504	1.407	1.145	£5,681
SOF	£65,426	15.867	8.513	£10,252	1.240	1.066	£9,616
EBR/GZR	£67,287	16.663	9.116	£12,113	2.036	1.669	£7,257
LDV/SOF	£69,467	16.694	9.139	£14,292	2.067	1.692	£8,448
2D/3D	£94,679	16.742	9.160	£39,504	2.115	1.713	£23,062

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

Table 6. Base case results – GT1a TE NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£27,836	19.504	12.806	-	-	-	-
BSC	£28,835	18.315	11.271	£999	-1.189	-1.535	Dominated
SMV	£34,982	20.224	14.203	£7,146	0.720	1.398	£5,112
2D/3D	£39,915	20.466	14.713	£12,079	0.962	1.907	£6,334
EBR/GZR	£42,298	20.383	14.578	£14,462	0.879	1.773	£8,159
LDV/SOF	£43,747	20.466	14.713	£15,911	0.962	1.907	£8,343
SOF	£45,111	20.170	14.198	£17,275	0.666	1.393	£12,403
DCV+SOF	£64,599	20.445	14.670	£36,763	0.940	1.864	£19,718

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

Table 7. Base case results – GT1b TN C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,884	15.478	7.709	-	-	-	-
SOF	£62,628	17.310	9.107	£7,743	1.833	1.398	£5,538
2D/3D	£64,947	17.596	9.327	£10,062	2.119	1.618	£6,217
SMV	£65,571	16.352	8.434	£10,687	0.874	0.725	£14,741
EBR/GZR	£67,714	17.640	9.356	£12,829	2.162	1.647	£7,787
LDV/SOF	£70,320	17.602	9.331	£15,436	2.125	1.622	£9,517

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 8. Base case results – GT1b TN NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,800	20.761	13.442	-	-	-	-
BSC	£30,513	19.183	11.404	£3,712	-1.578	-2.039	Dominated
LDV/SOF	£31,899	21.678	15.120	£5,099	0.917	1.678	£3,039
SMV	£37,062	21.326	14.499	£10,262	0.565	1.057	£9,710
2D/3D	£40,232	21.772	15.246	£13,432	1.011	1.804	£7,446
EBR/GZR	£41,963	21.746	15.209	£15,162	0.986	1.766	£8,585
SOF	£42,161	21.746	15.175	£15,361	0.985	1.733	£8,865
DCV+SOF	£65,018	21.747	15.201	£38,218	0.986	1.758	£21,739

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 9. Base case results – GT1b TE C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,008	14.805	7.577	-	-	-	-
SMV	£59,760	16.328	8.806	£5,751	1.522	1.229	£4,680
2D/3D	£62,754	16.892	9.285	£8,746	2.087	1.708	£5,122
EBR/GZR	£65,304	16.966	9.337	£11,296	2.160	1.760	£6,418
SOF	£66,777	15.661	8.363	£12,769	0.855	0.786	£16,253
LDV/SOF	£67,689	16.966	9.337	£13,681	2.160	1.760	£7,773

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

Table 10. Base case results – GT1b TE NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£28,407	19.458	12.730	-	-	-	-
BSC	£28,835	18.315	11.271	£428	-1.143	-1.459	Dominated
SMV	£35,177	20.208	14.178	£6,770	0.750	1.448	£4,676
2D/3D	£38,905	20.541	14.835	£10,499	1.083	2.105	£4,988
EBR/GZR	£40,595	20.522	14.804	£12,188	1.064	2.074	£5,877
LDV/SOF	£43,060	20.522	14.804	£14,654	1.064	2.074	£7,066
SOF	£44,393	20.229	14.293	£15,987	0.771	1.564	£10,225
DCV+SOF	£63,650	20.522	14.796	£35,244	1.064	2.066	£17,060

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

Table 11. Base case results – GT4 TN C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,599	15.526	7.741	-	-	-	-
SOF	£63,401	17.181	9.018	£8,802	1.655	1.277	£6,894
SMV	£65,380	16.384	8.456	£10,781	0.858	0.714	£15,095
EBR/GZR	£68,555	17.498	9.260	£13,956	1.973	1.518	£9,193
LDV/SOF	£70,941	17.498	9.259	£16,342	1.972	1.518	£10,765
DCV/PR	£84,350	17.665	9.301	£29,750	2.139	1.560	£19,076
2D/3D	£93,333	17.544	9.282	£38,734	2.018	1.541	£25,138

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 12. Base case results – GT4 TN NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,580	20.781	13.473	-	-	-	-
BSC	£30,513	19.183	11.404	£3,932	-1.598	-2.069	Dominated
SMV	£36,693	21.360	14.550	£10,113	0.579	1.077	£9,388
2D/3D	£37,785	21.757	15.225	£11,204	0.976	1.752	£6,396
EBR/GZR	£42,389	21.707	15.150	£15,809	0.926	1.677	£9,427
DCV/PR	£58,178	21.817	15.207	£31,598	1.036	1.735	£18,217

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 13. Base case results – GT4 TE C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,551	14.722	7.517	-	-	-	-
SMV	£61,311	16.091	8.633	£6,760	1.368	1.116	£6,055
SOF	£65,426	15.867	8.513	£10,875	1.145	0.997	£10,911
EBR/GZR	£67,287	16.663	9.116	£12,736	1.940	1.600	£7,962
LDV/SOF	£69,467	16.694	9.139	£14,916	1.972	1.622	£9,194
DCV/PR	£82,894	16.859	9.178	£28,343	2.136	1.662	£17,054
2D/3D	£91,857	16.749	9.164	£37,306	2.027	1.647	£22,645

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

Table 14. Base case results – GT4 TE NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£27,836	19.504	12.806	-	-	-	-
BSC	£28,835	18.315	11.271	£999	-1.189	-1.535	Dominated
SMV	£34,982	20.224	14.203	£7,146	0.720	1.398	£5,112
2D/3D	£37,220	20.466	14.713	£9,384	0.962	1.907	£4,920
EBR/GZR	£42,298	20.383	14.578	£14,462	0.879	1.773	£8,159
LDV/SOF	£43,747	20.466	14.713	£15,911	0.962	1.907	£8,343
DCV/PR	£57,873	20.515	14.664	£30,037	1.010	1.859	£16,160
DCV+SOF	£64,599	20.445	14.670	£36,763	0.940	1.864	£19,718

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

2 The technology

2.1 Description of the technology

Brand name: ZEPATIER®

Generic name: Elbasvir/Grazoprevir (EBR/GZR)

Therapeutic class: Elbasvir is an HCV NS5A inhibitor and grazoprevir is an HCV NS3/4A protease inhibitor. Anticipated BNF category "Chronic hepatitis C" (05.03.03.02).

Brief overview of mechanism of action:

EBR/GZR combines two DAA agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV viral replication at multiple points.

EBR is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. GZR is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, GZR inhibited the proteolytic activity of the recombinant NS3/4A protease enzymes from HCV genotypes 1a, 1b, 3 and 4a with IC50 values ranging from 4 to 690 pM.

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 Current UK regulatory status

- Marketing Authorisation Application submitted to EMA: 3rd July 2015
- CHMP positive opinion: Expected 26th May 2016
- Estimated date of Marketing Authorisation: August 2016

2.2.2 Indication in the UK

Zepatier (EBR/GZR) will be indicated for the treatment of CHC adults with GT1a, GT1b, and GT4 infections.

2.2.3 Anticipated restrictions or contraindications that are likely to be included in the draft summary of product characteristics (SmPC)

Please refer to the draft SmPC in Appendix 1.

2.2.4 Draft SmPC

The draft SmPC has been included in Appendix 1. Please note this draft SmPC may be subject to change as the regulatory review process is ongoing. MSD will forward the final SmPC immediately upon receipt.

2.2.5 Draft EMA assessment report

The EMA assessment report is currently unavailable. MSD anticipates the report following CHMP opinion and will forward this upon receipt. As soon as MSD in receipt of the draft version we will forward.

2.2.6 Summary of the main issues discussed by the regulatory authorities

Please see section 2.2.5 above.

2.2.7 Anticipated date of availability in the UK

The anticipated launch date following EMA regulatory approval is August 2016.

2.2.8 Details of regulatory approval outside of the UK

EBR/GZR has received regulatory approval in the following countries on the following dates:

- USA: Food and Drug Administration (FDA) approval on January 28th 2016.

  ZEPATIER is indicated with or without ribavirin for the treatment of CHC virus genotypes 1 or 4 infection in adults

- Puerto Rico: FDA approval on February 1st 2016.

  ZEPATIER is indicated with or without ribavirin for the treatment of CHC virus genotypes 1 or 4 infection in adults

- Canada: Notice of Compliance by Health Canada on January 19th 2016.

  ZEPATIER is indicated for the treatment of CHC genotypes 1, 3, or 4 infections in adults.

- Switzerland: Swiss Agency for Therapeutic Products on April 1st 2016.

  ZEPATIER® is indicated for the treatment of CHC of genotype 1 and 4 in adults.

2.2.9 Other health technology assessments in the UK

MSD will submit to the Scottish Medicines Consortium (SMC) in July 2016 for the same licensed indication presented within this submission.

2.3 Administration and costs of the technology

Table 15. Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Film-coated tablets	Draft SmPC (see appendix 1)
Acquisition cost (excluding VAT) *	List price: 28-day pack = £12,166.67 The maximum price payable within NHS Framework Agreements between MSD and CMU is: 28-day pack = [redacted]	MiMs[16]
Method of administration	Oral	Draft SmPC
Doses	Single tablet (FDC) of 50mg EBR and 100mg GZR	Draft SmPC
Dosing frequency	Once daily	Draft SmPC
Average length of a course of treatment	Treatment duration is for 12 weeks	Draft SmPC
Average cost of a course of treatment	EBR/GZR only: 12 weeks: £36,500 ([redacted] based on maximum price payable within NHS Framework Agreement between MSD and CMU, submitted 11th April 2016).	NA
Anticipated average interval between courses of treatments	Not applicable	Draft SmPC
Anticipated number of repeat courses of treatments	Not applicable	Draft SmPC
Dose adjustments	No dose adjustments are recommended	Draft SmPC
Anticipated care setting	EBR/GZR is anticipated to be initiated in secondary care, and administered at a patients' home without supervision	NA

* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

2.4 Changes in service provision and management

2.4.1 Additional tests or investigations needed

No additional tests or investigations are required further to the usual tests undertaken in current clinical practice. No diagnostic test is required to identify the population for whom EBR/GZR is indicated and no particular administration for the technology is required.

2.4.2 Main resource use to the NHS associated with the technology being appraised

Similar to the existing DAA treatments, the main resource use associated with EBR/GZR is anticipated to be related to monitoring and testing of patients while on treatment and following the completion of therapy.

The treatment of CHC is managed by multidisciplinary teams (MDTs) through established operational delivery networks (ODNs) in the NHS. EBR/GZR will be initiated largely in the outpatient setting of established ODNs and will be commissioned by NHS England (NHSE) specialised services.[17]

2.4.3 Additional infrastructure in the NHS

No additional infrastructure is necessary in the NHS for the implementation of EBR/GZR in clinical practice.

2.4.4 Extent that the technology will affect patient monitoring compared with established clinical practice in England

As with other all-DAA regimens, EBR/GZR is an IFN-free regimen, there is no requirement for additional monitoring at specific time points to identify the possibility of achieving SVR, and the potential for extending the duration of therapy is minimised. Furthermore, AEs rates observed in the clinical trial programme were low, which negates the need for extensive monitoring.

2.4.5 Concomitant therapies administered with the technology

MSD anticipates the use of EBR/GZR in line with the EMA label i.e. EBR/GZR alone for 12 weeks for the majority of patients. Note, that the duration of therapy may be increased to 16 weeks in combination with ribavirin at the discretion of physicians.

2.5 Innovation

2.5.1 State whether and how the technology is a 'step-change' in the management of the condition

MSD believes that treatment options able to provide a high level of clinical effectiveness in addition to minimal AEs are an attractive proposition. In patients diagnosed with CHC complicated by severe renal disease (eGFR; <30mL/min/1.73m^2) or ESRD there is a significant unmet clinical need, as there are limited treatment options currently available. A paucity of efficacy data for currently available DAAs in patients with creatinine clearance (CrCl) <30 mL/min and poor tolerability of existing regimens, i.e. RBV-containing regimens, related to increased risk of AE, may result in many dialysis patients remaining untreated. The product label of EBR/GZR does not require dose adjustment with regard to any degree of renal impairment including patients with ESRD receiving haemodialysis or peritoneal dialysis.

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

3.1 Brief overview of the disease/condition for which the technology is being used

Hepatitis C virus is a blood-borne virus that primarily causes infection of the liver. It is one of the worldwide leading causes of liver disease. Historically, the primary mode of transmission was through contaminated blood products, syringes, needles, and/or medical equipment. [18] The implementation of the "blood product safer injections practices" has meant that these modes of transmission are now rare in developed countries. [19, 20] The primary source of new infections in these countries is among people who actively inject drugs (needle sharing). It is estimated that around 90% of new HCV infections in UK (England) are in people who inject drugs (PWIDs).[21] Although the acute HCV infection may resolve, chronic HCV occurs in up to 80% of infected patients.[2] The manifestation of chronic HCV may take up to 30 years to become evident, thus a large proportion of those infected with HCV remain unaware of their disease status; and it is estimated that ~48% of patients are undiagnosed. [2, 9] Untreated HCV patients may transmit the virus to others and are at risk of developing liver inflammation with subsequent fibrosis and cirrhosis. CHC is categorised according to the extent of liver damage (Metavir score), i.e. mild (F0-F1), moderate (F2-F3) or severe (severe refers to cirrhosis, F4). The proportion of patients with chronic infection who develop cirrhosis is ~21%.[9] If the disease is left untreated cirrhosis can continue to progress to a decompensated state; this is where the remaining functional liver can no longer compensate for degree of fibrosis, and a liver transplant is typically required at this point. A small percentage of people with chronic HCV (i.e. 2-4%)[3] and cirrhosis also develop HCC. Patients diagnosed with HCC have a 33% probability of death during the first year after diagnosis, [22] and may also require a liver transplant. The probability of receiving a liver transplant following a diagnosis of either decompensated cirrhosis or HCC is estimated at ~2%. [23] HCV patients are at increased risk of developing CKD and ESRD compared to patients not infected with HCV via a number of mechanisms that include accelerated atheroma development and renal inflammation.[24, 25]

An ~185 million people around the world are infected with HCV, of whom 350,000 die each year.[3] In the UK, an ~214,000 individuals are chronically infected with HCV, of which ~160,000 people are infected in England alone.[8] There are 6 major genotypes and several subtypes of the HCV; the prevalence of each varies geographically. In the UK, GT1 and GT3 are equally distributed accounting for 90% of HCV infected patients, GT2 for 6%, GT4 for 4%

and, GT5 and GT6 for less than 1%.[9] Although antiviral treatments can successfully clear HCV in the majority of patients, and are available (approved for use) in the UK, it is estimated that only 28,000 patients in England were treated between 2006 and 2011. This represents 3% of those chronically infected per year.[21] Statistical modelling suggests that nearly 10,850 individuals are currently living with HCV-related cirrhosis or HCC in England. It is estimated that this figure will rise to 13,590 people by 2025 if patients remain unable to access the newly available treatment options.[21] It is difficult to ascertain the true prevalence of HCV as people can remain undiagnosed for many years and continue to transmit the infection. [26]

In current practice a blood test is performed to diagnose HCV infection; this confirms the presence of HCV antibodies. A positive test should always be confirmed by testing a second blood sample, due to false positives. If the antibody test is positive then polymerase chain reaction (PCR) testing is required to determine HCV RNA levels (viral load), in order to ascertain if the infection is active or not. Patients are also tested for HCV GT and subtype using the same PCR techniques. Most HCV patients will undergo an ultrasound scan or fibroscan of their liver to determine the disease stage (i.e. fibrosis stage) which will then inform the treatment they receive. Historically, the decision to treat was dependent on a liver biopsy that would determine disease stage; however, the latest guidelines allow for treatment to commence without this additional investigation for some patients. Liver biopsies are still performed in patients with HCV as they remain the gold-standard method of assessing the extent of liver damage.[27]

The primary goal of HCV therapy is to cure the infection. A SVR is defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion. Of note, SVR12 is now considered the gold standard as sufficient concordance with SVR24 has been established.[28]

The treatment landscape for HCV has rapidly changed with the approval of second-generation DAAs. These agents provide high levels of efficacy and an improved safety and tolerability profile compared with historic PR regimens. Despite advances in HCV treatment, there are still patient groups with significant unmet clinical need. There is a paucity of data in high risk populations such as: PWIDs, CKD, and patients with inherited blood disorders. Current NICE treatment regimens are not recommended in patients on dialysis, with or without severe renal disease, as well as in those with severe liver disease. It is of note that there is currently a lack of licensed regimens for the treatment of patients with HCV who have previously failed on new DAAs.

3.2 Effects of the disease/condition on patients, carers and society

HCV is potentially a life-threatening condition that affects patients both physically and emotionally. Patients have a lower QoL compared with the general population. Fatigue and depression are common in these patients, with lower mental and physical component summary scores compared to individuals not infected with HCV.[6, 29] In addition to increased medical costs/resource utilisation, a patient's QoL worsens with disease severity, i.e. patients with advanced liver disease compared with patients who have a lower stage of fibrosis.[30, 31] If left untreated a patients' deteriorating QoL could also have a negative impact on carers.

Due to the large number of patients infected by HCV, a significant budget impact associated with the treatment of HCV is expected, namely the implementation of the new DAAs recently approved by NICE. There has been an increase in the number of individuals throughout the UK being tested and diagnosed with HCV, which will likely result in more patients seeking access to treatment.[8] Indirect costs associated with HCV burden are not well quantified; this is most likely related to difficulties in estimating the prevalent population. However, a cohort simulation model has projected that using current treatment patterns, the overall prevalence of HCV in the UK would increase from 0.44% in 2010 to 0.61% in 2035. This equates to an increase of HCV infected individuals from 265,000 in 2010 to 370,000 in 2035 in the UK. This rise in prevalence would be associated with an increase in healthcare costs, from ~£82.7million in 2012 to ~£115 million in 2035. Productivity losses were estimated to rise from ~£184-367 million in 2010 to ~£210-427 in 2035, depending on whether the minimum wage (lower estimate) of median income (upper estimate) for the productive population was assumed in the model.[32]

Successful HCV treatment leads to an overall decrease in: liver-related morbidity, overall mortality, rates of HCC, and medical costs; along with increases in an individual's QoL, as well as, greater work and leisure capacity. In addition, greater benefits are gained with treatment earlier in the disease course for both morbidity and mortality compared to treatment later in the disease pathway. It would also decrease the risk of transmission among individuals.

3.3 Clinical pathway of care showing the context of the proposed use of the technology

The current clinical pathway of care takes into consideration multiple sources of information; these are described in section 3.5 and 3.6. It is MSD's understanding that current clinical practice is funded predominantly through specialised commissioning, which is managed

through a bi-annual tendering process across England. These recommendations and the tendering process have prioritised the treatment of patients with the highest level of unmet clinical need, namely those patients with DC and cirrhosis; aligned with NICE guidance.

The 2015 European Association for the Study of the Liver (EASL) guidelines [33] and 2016 UK consensus guidelines[34] are broadly aligned in terms of their recommendations for the use of direct-acting anti-viral therapies. Furthermore, NICE technology appraisals (TA) (TA75, 106, 200, 252, 253, 330, 331, 361, 363, 364, 365 [10-13, 35-41]) also provide recommendations based on cost-effectiveness evidence for the treatment of patients with HCV GT1, GT1a, GT1b, and GT4 relevant to this submission.

The EASL guidelines report that in more than 99% of patients who attain a SVR, their infection is cleared (treatment cure) (ref EASL guideline). The additional benefits of treating patients with CHC include; the resolution of liver disease in patients without cirrhosis, and for those patients with cirrhosis it is possible that hepatic fibrosis may regress and that the risk of complications such as hepatic failure and portal hypertension is reduced. The guidelines also suggest that the risk of HCC and all-cause mortality is significantly reduced, but not eliminated, in cirrhotic patients who clear their infection compared with untreated patients and those who have not achieved SVR [33, 42, 43].

Treatment choice is multifactorial and takes into account the: viral genotype and subtype, stage of liver disease, cirrhosis status, treatment experience, and previous therapy regimens. These considerations are inherently linked with treatment efficacy, which supports the clinical need for additional HCV treatment options.

Current treatment options include established treatments, such as PEG-IFN, telaprevir (TVR), and boceprevir (BOC); all of which are recommended by NICE and are summarised in Table 16. Most recently NICE have recommended the use of sofosbuvir (SOF), simeprevir (SMV), daclatasvir (DCV), ledipasvir-sofosbuvir (LDV/SOF), and ombitasvir/paritaprevir/ritonavir with (3D) or without dasabuvir (2D) within specific patient populations. These treatment options are stratified by treatment experience, cirrhosis stage, and GT subtype (Table 16). Only recommendations relevant to the decision problem have been included. Based on the available evidence and numerous recommendations described in section 3.5 and 3.6 it is clear that DAA therapies are the preferred treatment choice and reflect current clinical practice in both England and the UK as a whole.

Elbasvir/grazoprevir

EBR/GZR is an oral, once daily single FDC tablet regimen for the treatment (cure) of HCV in patients with GT1a, GT1b, or GT4 infections EBR/GZR can be administered for 12 weeks

irrespective of treatment experience and cirrhosis stage. EBR/GZR represents an IFN- and RBV-free treatment option for the majority of adult patients. It is anticipated that EBR/GZR will represent a preferred treatment option to IFN-containing regimens, including PEG-IFN, SOF/PEG-IFN, and SMV; this is supported by the recommendations of the clinical guidelines described in section 3.6. The ease of use associated with EBR/GZR could facilitate a simplified clinical offering compared with recent DAA recommendations that must take into consideration treatment experience and cirrhosis stage.

3.4 Information about the life expectancy of people with the disease or condition in England and the source of the data

If untreated, HCV can sometimes cause serious and/or life-threatening liver fibrosis, which is thought to occur over many years. However, with the availability of second generation DAAs it is often possible to cure the infection, and prevent disease progression. For the majority of patients it is possible to achieve a normal life expectancy.[17]

Limited data on life expectancy in HCV-infected individuals is available; however, an English cohort study [44] reported standardised mortality ratios three times higher than those expected in the general population. The increased risk of mortality was attributed to liver-related causes, and those patients with a drug-using lifestyle. Significant independent predictors of all-cause mortality were: age, sex, treatment experience, and liver biopsy fibrosis. Predictors of liver-related mortality are: age, treatment experience, liver biopsy fibrosis score, and mean alcohol consumption. HCV mortality was recorded on 23% of death certificates overall, and on 52% of those of patients dying from a liver-related cause. [44]

3.5 Details of relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being

NICE recently communicated (29th February 2016) that the proposed Hepatitis C clinical guideline has been put on hold with a publication date still to be confirmed. NICE has stated that technology appraisals (TA) continue to evaluate new pharmacological therapies and the role of the clinical guideline will be re-considered when these have been produced. The table below summarises all NICE TA for the currently available treatment options for patients diagnosed with CHC. In addition, NICE has also published public health guidance ‘Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection’; with an anticipated review date of December 2016[45] (Table 16).

Table 16. NICE guidance and technology appraisal recommendations for patients with hepatitis C.

Guidance/ TA number	Publication date	Title	Guidance recommendations wording is as per guidance documents including and reference to other section within the respective guidance document
NICE, CG	TBC	Hepatitis C	28 January 2016: NICE has taken the decision to continue to pause development. The guideline will be reconsidered when the future TAs have been produced.
PH43[45]	December 2012	HBV and HCV testing: people at risk of infection	This document provides the following recommendations relevant to patients with hepatitis C, with reference to the BHIVA and EASL guidelines. • Awareness-raising about hepatitis B and C among the general population • Awareness-raising for people at increased risk of hepatitis B or C infection • Developing the knowledge and skills of healthcare professionals and others providing services for people at increased risk of hepatitis B or C infection • Testing for hepatitis B and C in primary care • Testing for hepatitis B and C in prisons and immigration removal centres • Testing for hepatitis B and C in drugs services • Testing for hepatitis B and C in sexual health and genitourinary medicine clinics • Contact tracing • Commissioning locally appropriate integrated services for hepatitis B and C testing and treatment • Laboratory services for hepatitis B and C testing This guidance does not provide details on treatment for CHC.
TA365[13]	November 2015	3D or 2D for treating CHC	1.1 Ombitasvir–paritaprevir–ritonavir with or without dasabuvir is recommended, within its marketing authorisation, as an option for treating genotype 1 or 4 CHC in adults, as specified in table 1 (see TA365), only if the company provides ombitasvir–paritaprevir–ritonavir and dasabuvir at the same price or lower than that agreed with the Commercial Medicines Unit. 1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.
TA364[12]	November 2015	DCV for treating CHC	1.1 Daclatasvir is recommended as an option for treating CHC in adults, as specified in table 1 (see TA364), only if the company provides daclatasvir at the same price or lower than that agreed with the Commercial Medicines Unit. 1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.
TA363[11]	November 2015	LDV/SOF for treating CHC	1.1 LDV/SOF is recommended as an option for treating CHC in adults, as specified in table 1 (see TA363). **Ledipasvir–sofosbuvir** • GT1 without cirrhosis ○ TN 8 weeks – Recommended

Guidance/ TA number	Publication date	Title	Guidance recommendations wording is as per guidance documents including and reference to other section within the respective guidance document
			○ TE 12 weeks – Recommended • GT1 with compensated cirrhosis ○ TN 12 weeks – Recommended ○ TE 12 weeks – Recommended only if all the following criteria are met: Child–Pugh class A; platelet count of 75,000/mm^3 or more; no features of portal hypertension; no history of an HCV -associated decompensation episode; not previously treated with an NS5A inhibitor. • GT4 without cirrhosis ○ TE 12 weeks – Recommended • GT4 with compensated cirrhosis ○ TN 12 weeks – Recommended ○ TE 12 weeks – Recommended only if all the following criteria are met: Child–Pugh class A; platelet count of 75,000/mm^3 or more; no features of portal hypertension; no history of an HCV -associated decompensation episode; not previously treated with an NS5A inhibitor. 1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.
TA361[41]	October 2015	SMV+SOF for treating CHC GT 1 or 4	NICE is unable to make a recommendation about the use in the NHS of simeprevir in combination with sofosbuvir for treating genotype 1 or 4 CHC because no evidence submission was received from Janssen for the technology.
TA331[40]	February 2015	SMV+PR for treating CHC GT1 and 4	1.1 Simeprevir, in combination with peginterferon alfa and ribavirin, is recommended within its marketing authorisation as an option for treating genotype 1 and 4 CHC in adults. Simeprevir SmPC, accessed 1st March 2016 The following patient population, treatment regimen, and duration of therapy has been taken from Table 1, section 4.2 of the SmPC[46]. • Treatment-naïve, prior relapse and prior non-responder patients (including partial and null responders) with HCV genotype 1 or 4, with or without cirrhosis, with or without HIV co-infection; ○ OLYSIO+sofosbuvir (+/- ribavirin) ○ 12 weeks • Treatment-naïve and prior relapse patients with HCV genotype 1 or 4 • Patients with or without cirrhosis, who are not co-infected with HIV/or patients without cirrhosis, who are co-infected with HIV; ○ OLYSIO+peginterferon alfa+ribavirin; ○ 24 weeks treatment with OLYSIO must be initiated in combination with peginterferon alfa and

Guidance/ TA number	Publication date	Title	Guidance recommendations wording is as per guidance documents including and reference to other section within the respective guidance document
			ribavirin and administered for 12 weeks and then followed by an additional 12 weeks of peginterferon alfa and ribavirin. • Patients with cirrhosis, who are co-infected with HIV; ○ OLYSIO+peginterferon alfa+ribavirin; ○ 48 weeks treatment with OLYSIO must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 36 weeks of peginterferon alfa and ribavirin. • Patients described as prior non-responder (including partial and null responders) with HCV genotype 1 or 4, with or without cirrhosis, with or without HIV co-infection; ○ OLYSIO+peginterferon alfa+ribavirin; ○ 48 weeks treatment with OLYSIO must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 36 weeks of peginterferon alfa and ribavirin.
TA330[10]	February 2015	SOF for treating CHC	1.1 Sofosbuvir is recommended as an option for treating CHC in adults, as specified in table 1 (see TA 330). • SOF+PEG-IFN alfa+RBV ○ GT1 All – Recommended. ○ GT3 TN – Recommended only for people with cirrhosis. ○ GT3 TE –Recommended. ○ GT4, 5, 6 All – Recommended for people with cirrhosis. • SOF+RBV ○ GT2 TN – Recommended for people who are intolerant to or ineligible for interferon. ○ GT2 TE – Recommended. ○ GT3 TN – Only recommended for people with cirrhosis who are intolerant to or ineligible for interferon. ○ GT3 TE – Only recommended for people with cirrhosis who are intolerant to or ineligible for interferon.
TA253[39]	April 2012	BOC for treating CHC GT1	1.1 Boceprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of genotype 1 CHC in adults with compensated liver disease: • who are previously untreated **or** • in whom previous treatment has failed
TA252[38]	April 2012	TVR for treating CHC GT1	1.1 Telaprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of genotype 1 CHC in adults with compensated liver disease: • who are previously untreated **or** • in whom previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin has failed, including people whose condition has relapsed, has partially responded or did

Guidance/ TA number	Publication date	Title	Guidance recommendations wording is as per guidance documents including and reference to other section within the respective guidance document
			not respond.
TA200[37]	September 2010	PR for treating CHC	1.1 Combination therapy with peginterferon alfa (2a or 2b) and ribavirin is recommended as a treatment option for adults with CHC: • who have been treated previously with peginterferon alfa (2a or 2b) and ribavirin in combination, or with peginterferon alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed **or** • who are co-infected with HIV. 1.2 Shortened courses of combination therapy with peginterferon alfa (2a or 2b) and ribavirin are recommended for the treatment of adults with CHC who: • have a rapid virological response to treatment at week 4 that is identified by a highly sensitive test **and** • are considered suitable for a shortened course of treatment. 1.3 When deciding on the duration of combination therapy, clinicians should take into account the licensed indication of the chosen drug (peginterferon alfa-2a or peginterferon alfa-2b), the genotype of the hepatitis C virus, the viral load at the start of treatment and the response to treatment (as indicated by the viral load).
TA106[36]	August 2006	PR for treating mild CHC	1.1 Combination therapy, comprising peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin, is recommended, within the licensed indications of these drugs, for the treatment of mild CHC. 1.2 Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended, within the licensed indications of these drugs, for the treatment of mild CHC for people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated. 1.3 The decision on whether a person with mild CHC should be treated immediately or should wait until the disease has reached a moderate stage ('watchful waiting') should be made by the person after fully informed consultation with the responsible clinician. The decision to treat need not depend on a liver biopsy to determine the stage of the disease if treatment is initiated immediately. However, a biopsy may be recommended by the clinician for other reasons or if a strategy of watchful waiting is chosen. 1.4 This recommendation has been updated and replaced by NICE technology appraisal guidance 200 ('Peginterferon alfa and ribavirin for the treatment of CHC'). 1.5 This recommendation has been updated and replaced by NICE technology appraisal guidance 200 ('Peginterferon alfa and ribavirin for the treatment of CHC'). 1.6 This recommendation has been partially updated and replaced by NICE technology appraisal guidance 300 ('Peginterferon alfa and ribavirin for treating CHC in children and young people'). There is insufficient evidence to recommend combination therapy or monotherapy with peginterferon alfa for people who have had a liver transplant.
TA75[35]	January 2004	IFN and RBV for treating CHC	1.1 Combination therapy with peginterferon alfa and ribavirin is recommended within its licensed indications for the treatment of people aged 18 years and over with moderate to severe CHC, defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation. Separate

Guidance/ TA number	Publication date	Title	Guidance recommendations wording is as per guidance documents including and reference to other section within the respective guidance document
			recommendations for treating CHC in children and young people with peginterferon alfa and ribavirin have been published in NICE technology appraisal guidance 300 ('Peginterferon alfa and ribavirin for treating CHC in children and young people'). 1.2 People with moderate to severe CHC are suitable for treatment if they have: • not previously been treated with interferon alfa or peginterferon alfa, or • been treated previously with interferon alfa (as monotherapy or in combination therapy), and/or • this part-recommendation has been updated and replaced by NICE technology appraisal guidance 200. 1.3 People currently being treated with interferon alfa, either as combination therapy or monotherapy, may be switched to the corresponding therapy with peginterferon alfa. 1.4 Treatment for the groups identified in Sections 1.1 and 1.2 should be as follows. • People infected with hepatitis C virus (HCV) of genotype 2 and/or 3 should be treated for 24 weeks. • For people infected with HCV of genotype 1, 4, 5 or 6, initial treatment should be for 12 weeks. Only people showing, at 12 weeks, a reduction in viral load to less than 1% of its level at the start of treatment (at least a 2-log reduction, see Section 4.1.2.5) should continue treatment until 48 weeks. For people in whom viral load at 12 weeks exceeds 1% of its level at the start of treatment, treatment should be discontinued. • People infected with more than one genotype that includes one or more of genotypes 1, 4, 5, or 6 should be treated as for genotype 1. (Recommendation 4.1 still applies for people who are treated with standard courses of combination therapy, but has been replaced by NICE technology appraisal guidance 200 (TA200) for people who are eligible for shortened courses of combination therapy (as described in recommendation 1.2 of TA200). 1.5 People satisfying the conditions in Sections 1.1 and 1.2 but for whom ribavirin is contraindicated or is not tolerated should be treated with peginterferon alfa monotherapy. Regardless of genotype, individuals should be tested for viral load at 12 weeks, and if the viral load has reduced to less than 1% of its level at the start of treatment, treatment should be continued for a total of 48 weeks. If viral load has not fallen to this extent, treatment should stop at 12 weeks. 1.6 People for whom liver biopsy poses a substantial risk (such as those with haemophilia, or those who have experienced an AE after undergoing a previous liver biopsy), and people with symptoms of extra-hepatic HCV infection sufficient to impair quality of life, may be treated on clinical grounds without prior histological classification.

Abbreviations. CHC, chronic hepatitis C; GT, genotype; HCV, hepatitis C virus; PEG IFN alpha, pegylated interferon alpha; RBV, ribavirin; SOF, sofosbuvir; SmPC, summary of product characteristics; TA, technology appraisal; TE, treatment experienced; TN, treatment naïve

3.6 Details of other clinical guidelines and national policies

Described below are clinical guidelines, clinical consensus documents, and a NHSE clinical commissioning policy (CCP)[47]. There is overlap between the European and UK clinical consensus guidelines[34]. The recommendations advocate the use of IFN-free treatment options, and anticipate that patients who are HCV and HIV co-infected should achieve comparable SVR rates compared with those patients who are mono-infected with HCV. The treatment options recommended within the current NHSE clinical commissioning policy and recent ODN consensus meeting (published on the British Association for the Study of Liver (BASL) website) also advocate IFN-free treatment options[48]. However, some considerations are outside of NICE recommendations; as described in section 3.5.

European Association for the Study of the Liver (EASL) – Recommendations on the treatment of hepatitis C 2015[33]

The EASL 2015 clinical guidelines outline several treatment options for patients with CHC GT1-GT6. However, only those treatment regimens relevant to the decision problem i.e. GT1a, GT1b, and GT4, have been considered within this submission (Table 17). The guideline recommendations also include:

- Treatment for HCV mono-infected patients is identical to those patients who are co-infected with HCV and HIV
- Notwithstanding the respective costs of these options, IFN-free regimens are the best option when available in HCV-mono-infected and HIV co-infected patients without cirrhosis or with compensated/decompensated cirrhosis, because of their virological efficacy, ease of use and tolerability.
- The IFN-free treatment regimens can be used in HIV co-infected patients as in patients without HIV infection, as the virological results of therapy are identical.
- Full details treatment options relating to GT1a, GT1b, and GT4 are summarised in Table 17 below.

Table 17. EASL 2015, adaptation of treatment recommendations for patients with a diagnosis of HCV GT1a, GT1b, and GT4

Genotype	Recommendation details (regimen, duration, and considerations)
1a	**IFN-containing regimens** • PEG IFN alpha+RBV+SOF; 12 weeks • PEG IFN alpha+RBV+SMV; 12 weeks+PEG IFN+RBV 12 weeks (total duration 24 weeks); TN or TE prior relapser patients including cirrhotic patients • PEG IFN alpha+RBV+SMV; 12 weeks+PEG IFN+RBV 36 weeks (total duration 48 weeks); TE prior partial or null responders including cirrhotic patients

Genotype	Recommendation details (regimen, duration, and considerations)
	IFN- free containing regimens Sofosbuvir+ledipasvir with or without Ribavirin • SOF+ LDV; 12 weeks; TN or TE, NC • SOF+ LDV; 12 weeks; TN or TE, NC if baseline RNA is below 6 million IU/ml • SOF+ LDV+RBV; 12 weeks; TN or TE, compensated cirrhosis • SOF+ LDV; 24 weeks; in patients with compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin. • SOF+ LDV+RBV; 24 weeks; TE compensated cirrhosis, and negative predictors of response i.e. platelet count. Ombitasvir, paritaprevir, ritonavir, and dasabuvir • 3D+RBV; 12 weeks; NC • 3D+RBV; 24 weeks; C
1b	**IFN-free containing regimens** Ombitasvir, paritaprevir, and ritonavir • 3D+RBV; 12 weeks; NC • 3D+RBV; 12 weeks; C
4	**IFN-containing regimens** • PEG IFN alpha+RBV+SOF; 12 weeks • PEG IFN alpha+RBV+SMV; 12 weeks+PEG IFN+RBV 12 weeks (total duration 24 weeks); TN or TE prior relapser patients including cirrhotic patients • PEG IFN alpha+RBV+SMV; 12 weeks+PEG IFN+RBV 36 weeks (total duration 48 weeks); TE prior partial or null responders including cirrhotic patients **IFN-free containing regimens** Sofosbuvir+ledipasvir with or without Ribavirin • SOF+ LDV; 12 weeks; TN or TE, NC • SOF+ LDV+RBV; 12 weeks; TN or TE, compensated cirrhosis • SOF+ LDV; 24 weeks; in patients with compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin. • SOF+ LDV+RBV; 24 weeks; TE compensated cirrhosis, and negative predictors of response i.e. platelet count. Ombitasvir, paritaprevir, ritonavir, and dasabuvir • 3D without dasabuvir+RBV; 12 weeks; NC • 3D without dasabuvir+RBV; 24 weeks; C Sofosbuvir+simeprevir • SOF+SMV; 12 weeks • SOF+SMV+RBV • SOF+SMV+RBV; 24 weeks; patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered Sofosbuvir+daclatasvir • SOF+DCV; 12 weeks • SOF+DCV+RBV • SOF+DCV; 24 weeks; in patients with cirrhosis with contra-indications to the use of ribavirin; this extended duration must be considered.

Abbreviations. 3D, Ombitasvir, paritaprevir, ritonavir, and dasabuvir; C, cirrhotic; DCV, daclatasvir; LDV, ledipasvir; NC, non-cirrhotic; PEG IFN alpha, pegylated interferon alpha; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naïve

UK consensus guidelines – hepatitis C management and direct acting-anti-viral therapy

The 2014 UK consensus guidelines, a review article, presented evidence for the use of novel agents for the treatment of HCV [34]. The findings of this review focused on the use of SOF, SMV, and PR. The authors concluded that the HCV landscape has evolved, and moved into a new era of IFN-free regimens that represent a reality for some situations. The report highlighted significant improvements in terms of SVR rates, and less significant side effects, and reduced patient discontinuation rates. However, the group noted that treatment choice depends on multiple factors, including: efficacy, safety, patient characteristics, patient and clinician preference, and treatment cost. Treatment recommendations are summarised in Table 18 below. Furthermore, the UK consensus guidelines present the following recommendations for consideration:

- Co-infected HIV/HCV patients with well-controlled HIV disease can be considered for therapy according to mono-infected recommendations. Caution should be exercised around drug–drug interactions. Management of such patients should be undertaken by team's expert in both infections.
- Urgent consideration for therapy should be given to patients with HCV-induced liver failure; in those ineligible or unable to access clinical trials the treatment outcome data should preferably be recorded in a national registry. Such patients should be managed in specialist centres experienced in both HCV treatment and the management of liver failure. Patients pre- or post-transplant for HCV could be considered for therapy by expert centres.

Table 18. Summary of recommendations for patients with HCV infections GT1a, GT1b, and GT4; adapted from table 1 UK consensus guidelines.

Genotype	Recommendation details (regimen, duration, and considerations)
1a	**Treatment Naïve** • PEG IFN alpha+RBV+SOF, 12 weeks • SMV, 12 weeks+PEG IFN+RBV, 24 weeks **Treatment experienced** • PEG IFN alpha+RBV+SOF, 12 weeks • SMV, 12 weeks+PEG IFN+RBV, 24 or 48 weeks **Cirrhosis of severe fibrosis** • PEG IFN alpha+RBV+SOF, 12 weeks
1b	**Treatment Naïve** • PEG IFN alpha+RBV+SOF, 12 weeks • SMV, 12 weeks+PEG IFN+RBV, 24 weeks **Treatment experienced** • PEG IFN alpha+RBV+SOF, 12 weeks • SMV, 12 weeks+PEG IFN+RBV, 24 or 48 weeks

Genotype	Recommendation details (regimen, duration, and considerations)
4	**Treatment Naïve** • PEG IFN alpha+RBV+SOF, 12 weeks • SMV, 12 weeks+PEG IFN+RBV, 24 or 48 weeks **Treatment experienced** • PEG IFN alpha+RBV+SOF, 12 weeks • SMV, 12 weeks+PEG IFN+RBV, 24 or 48 weeks **Cirrhosis of severe fibrosis** • PEG IFN alpha+RBV+SOF, 12 weeks

Abbreviations. PEG IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir

The British HIV Association (BHIVA) - Guidelines for the management of hepatitis viruses in adults infected with HIV 2013 [49]

The BHIVA clinical guideline for the management of hepatitis viruses in adults infected with HIV was published in 2013, and updated in 2014. This guideline aims to provide guidance on the best clinical practice in the treatment and management of adults with HIV and viral hepatitis co-infection, and should be used in conjunction with other hepatitis guidelines. Several recommendations have been summarised below, this is not a comprehensive list:

- BHIVA recommend that patients with a CD4 cell count less than 350cells/μL commence antiretroviral treatment (ART) to allow a degree of immune recovery before HCV therapy is initiated.

- BHIVA recommend commencing ART to optimise immune status before anti-HCV therapy is initiated when the CD4 count is 350–500 cells/μL unless there is an urgent indication for anti-HCV treatment when ART should be commenced as soon as the patient has been stabilised on HCV therapy.

- BHIVA advocate the use of direct acting antivirals (DAA) for the treatment of HCV, with careful consideration given to potential drug-drug interactions. All drug interactions should be checked with an expert source (e.g. www.hivdruginteractions.org).

In addition to the above, there are a number of HCV-specific recommendations that focus on the decision making process regarding a patient's treatment, i.e. regular testing/GT identification, the staging of liver disease using non-invasive methods, and the consideration given to the drug-drug interaction profile of HIV/HCV medicines.

Consensus meeting for the treatment recommendations for the management of patients with Chronic HCV Infection – February 2016[48]

On the 29th February 2016, the BASL published the findings of a consensus meeting held in January 2016. This meeting was chaired by Prof Graham Foster and included treating physicians from the ODN, who are heavily involved with treatment of patients with HCV; pharmaceutical representatives were also in attendance. The recommendations summarised in Table 19 below are relevant to the current submission i.e. GT1a, GT1b, and GT4 and include both NICE approved and unapproved recommendations. The group were clear that the price of treatment varied considerably, and that clinicians should take due regard to budgetary impact in addition to the individual patient requirements.

The group also mentioned that the ODNs would encourage NHSE to make EBR/GZR and Sofosbuvir/Velpatasvir available within their licensed indications should they become available during the lifetime of these recommendations.

Table 19. Consensus meeting treatment guidelines GT1a, GT1b, and GT4 [48]

Genotype	Recommendation details (regimen, duration, and considerations)
1a	**Treatment Naïve** • LDV/SOF; 8 weeks, NC patients • LDV/SOF +/- RBV; 12 weeks, C patients (the inclusion or not of RBV is not NICE recommended, and should be considered for those patients who are more likely to have a poor response i.e. prior null responders) • OMB+PAR+ DAS+RBV; 12 weeks, NC patients • OMB+PAR+DAS+RBV; 12 weeks, C patients with Child Pugh A only (In patients at low risk of treatment failure ribavirin may be omitted. 24 weeks in genotype 1a prior null responders, otherwise 12 weeks; this differs from NICE who recommend 24 weeks for all) **Treatment experienced** • LDV/SOF; 12 weeks, NC patients • LDV/SOF +/- RBV; 12 weeks, C patients (the inclusion or not of RBV is not NICE recommended, and should be considered for those patients who are more likely to have a poor response i.e. prior null responders) • OMB+PAR+ DAS+RBV; 12 weeks, NC patients • OMB+PAR+DAS+RBV; 12/24 weeks, C patients with Child Pugh A only (In patients at low risk of treatment failure ribavirin may be omitted 24 weeks in genotype 1a prior null responders, otherwise 12 weeks; this differs from NICE who recommend 24 weeks for all) Patients with liver decompensation: LDV/SOF+RBV 12; (this is not NICE approved)
1b	**Treatment Naïve** • LDV/SOF; 8 weeks, NC patients • LDV/SOF +/- RBV; 12 weeks, C patients (the inclusion or not of RBV is not NICE recommended, and should be considered for those patients who are more likely to have a poor response i.e. prior null responders) • OMB+PAR+DAS; 12 weeks, NC patients • OMB+PAR+DAS+RBV; 12 weeks, C patients with Child Pugh A only (In patients at low risk of treatment failure ribavirin may be omitted. 24 weeks in genotype 1a prior null responders, otherwise 12 weeks; this differs from NICE who recommend 24 weeks for all)

Genotype	Recommendation details (regimen, duration, and considerations)
	Treatment experienced • LDV/SOF; 12 weeks, NC patients • LDV/SOF +/- RBV; 12 weeks, C patients (the inclusion or not of RBV is not NICE recommended, and should be considered for those patients who are more likely to have a poor response i.e. prior null responders) • OMB+PAR+DAS; 12 weeks, NC patients • OMB+PAR+DAS+RBV; 12/24 weeks, C patients with Child Pugh A only (In patients at low risk of treatment failure ribavirin may be omitted 24 weeks in genotype 1a prior null responders, otherwise 12 weeks; this differs from NICE who recommend 24 weeks for all) Patients with liver decompensation: LDV/SOF+RBV 12; (this is not NICE approved)
4	**Treatment Naïve** • OMB+PAR +/- RBV; 12 weeks, NC patients (In exceptional circumstances, can consider SOF+DAC+RBV or 12W LDV/SOF (Not NICE approved), in those patients in whom drug-drug interactions with OMB+PAR+RBV are considered a potential concern. • LDV/SOF; 12 weeks, C patients • OMB+PAR+RBV; 12 weeks **Treatment experienced** • LDV/SOF; 12 weeks, NC patients • OMB+PAR+RBV; 12 week, NC patients • LDV/SOF +/- RBV; 12 weeks, C patients (use or not of RBV is not NICE recommended) • OMB+PAR+RBV; 24 weeks, C patients (For patients who are at low risk of treatment failure consideration should be given to 12 weeks treatment) Patients with liver decompensation: LDV/SOF+RBV 12; (this is not NICE approved)

Abbreviations. OMB, Ombitasvir; PAR, paritaprevir; DAS, dasabuvir; LDV/SOF, harvoni; RBV, ribavirin; C, cirrhotic patients; NC, non-cirrhotic patients

NHSE Clinical commissioning policy[47]

In June 2015 NHSE published the CCP statement: 'Treatment of chronic Hepatitis C in patients with cirrhosis'. This policy outlines treatment options that will be routinely commissioned by NHSE for the treatment of CHC with cirrhosis. It should be noted, and the policy statement makes clear, that several aspects of these recommendations, i.e. treatment duration, are outside of the EMA license for the respective treatment options.

This clinical commissioning policy does not cover the treatment of patients who are described as non-cirrhotic. At present, there is a lack of clarity regarding the role of this clinical commissioning policy in relation to the recent NICE recommendations outlined in TA363, TA364, and TA365, which received mandatory funding as of the 23rd February 2016. MSD will be presenting comparisons according to the NICE recommended treatment as outlined in Table 16 above.

3.7 Issues relating to current clinical practice, including variations or uncertainty about established practice

DAAs constitute current clinical practice across England. However, it is unclear whether the recent NICE TAs will supersede the existing NHSE CCP that has been in effect since June 2015 (see section 3.6). The most recent NICE TAs (i.e. SOF, LDV/SOF, 2D/3D, DCV) support the restricted recommendations of the current NHSE policy. However, NICE have also made recommendations relating to the treatment of non-cirrhotic patients. It is of note that NICE also stipulate the treatment of patients according to the highest level of unmet clinical need, which should be decided by MDT in conjunction with the ODN established by NHSE. NHSE have committed to doubling the number of treatments to ~10,000 patients in 2016-17.[50]

The availability of additional HCV treatment options is essential for both patients and clinicians, as both the treatment regimen and duration are dependent on prior treatment experience and cirrhosis stage. In order to facilitate simple prescribing and enhanced patient compliance it is important to have treatments that offer simple treatment durations, and are also able to demonstrate improved efficacy and safety. EBR/GZR is an IFN- and RBV-free licensed DAA that benefits from a simple treatment duration (12 weeks) for patients with GT1a, GT1b and GT4 infection (see appendix 1).

3.8 Equality issues

The 2015 Public Health England report shows that the majority of infected persons are from marginalised and under-served groups in society, namely PWIDs. In England and Wales, it is estimated that 50% of PWIDs are thought to be infected with HCV.[8] Prisons are recognised to contain a higher HCV prevalent population where it would be important to tackle inequalities, as well as in minority ethnic populations.[21]

There is also a stigma associated with HCV-CKD patients on haemodialysis. When attending for treatment they are dialysed in a separate 'special' room with different equipment- this creates an obvious and uncomfortable separation between them and other patients, and may ultimately be the source of newly-acquired infections if the equipment is not properly sterilised.

Due to recent developments in HIV care, patients can expect a life expectancy comparable to a non-HIV infected patient whilst maintaining a suppressed viral load. This has implications for their own general health and that of their partner. However, HIV/HCV co-infected patients are more likely to disclose their HIV status than their HCV status to sexual partners due to perceived stigma of HCV and lack of HCV awareness.[51]

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Search strategy

A comprehensive systematic literature search (SLR) was conducted according to a previously prepared protocol; this was designed to identify relevant studies to inform both direct and indirect comparisons between EBR/GZR and the interventions outlined in the final scope. Further details are reported below.

4.1.2 Search strategy: description of the search strategy

A comprehensive search of the literature was conducted using the following databases: Embase, Medline, and Cochrane Central Register of Controlled Trials. These databases were searched on the 12th of January 2016 using the OVID platform. The proceedings of the annual conferences of the American Association for the Study of Liver Diseases (AASLD), and the EASL were manually searched. These searches were restricted to conferences in 2014 and 2015 as it was expected that any earlier abstracts would now be available as full publication. Further, a manual search of treatment labels and included bibliographic reference lists to identify any further studies that were eligible for inclusion. To identify any ongoing clinical trials, the International Clinical Trials Registry Platform (ICTRP) was also searched.

The search strategy was pre-specified in terms of population, interventions, comparisons, outcomes, and study design as reported in the PICOS table in Appendix 2. Please note that GT3 and GT6 were initially included within the SLR, but were subsequently excluded from the evidence synthesis based on the anticipated EMA license. The search strategy for each database is reported in Appendix 2 with an adapted version of the Scottish Intercollegiate Guidelines Network's (SIGN) search filter for randomised-controlled clearly highlighted.

4.1.3 Study selection

Description of the inclusion and exclusion selection criteria, language restrictions, and the study selection process

Electronic databases/conference/trial registry searches

Two investigators working independently reviewed all abstracts and conference proceedings identified by the literature/conference searches. The same two investigators independently reviewed all articles included during screening as full-text articles. Discrepancies between the investigators were resolved by involving a third investigator and coming to consensus.

Summarised in Table 20 are the hierarchical inclusion/exclusion criteria applied during abstract and full-text screening.

Table 20. Hierarchical inclusion/exclusion criteria for SLR

Rank	Clinical effectiveness criteria	Reason for inclusion	Reason for exclusion	Hierarchy of exclusion rationale
1	Language	English only	Other languages	Non-English language publications were expected to include populations not relevant to the decision problem.
2	Study design	Randomized controlled trials and controlled clinical trials with at least one arm assessing an intervention of interest, non-randomized clinical trials, including single-arm prospective clinical trials assessing an intervention of interest	Review, editorial, letter, comment, meta-analysis, phase 1 studies, in-vitro studies	See comment above relating to comparators.
3	Populations	Not chronically infected with HCV genotypes 1 or 4, not adult population (≥18 years of age)	Not chronically infected with HCV genotypes 1 or 4, not adult population (≥18 years of age)	EBR/GZR is not licensed for use outside of these populations.
4	Interventions	Interferon-free regimens: EBR/GZR (+/- RBV) LDV/SOF +/- RBV OMB+PAR/r +/- DAS +/- RBV DCV+SOF +/- RBV SOF+RBV Interferon-containing regimens: DCV+PR BOC+PR TVR+PR SMV+PR SOF+PR	Other DAA combinations, with or without PR	Studies were not excluded based on dose or duration at the literature search stage. However, in the indirect treatment comparison only trial arms with NICE approved regimens were included.
5	Outcomes	SVR12, SVR24, DAE, OAE, aneamia, pruritus, nausea, neutropenia, rash, thrombocytopenia.	RVR, eRVR, vRVR, EVR	SVR at 12 and 24 weeks post treatment are the primary efficacy outcomes in trials of treatments for HCV.
5	Comparators	All	None	Single arm studies were also included, as were studies comparing different regimens of the same DAA combination.

Abbreviations. BOC, boceprevir; DAA, direct acting antiviral; DAE, discontinuation related to AE; DCV, daclatasvir; DAS, dasabuvir; EBR, Elbasvir; eRVR, extended rapid viral response; EVR, early viral response; GZR, grazoprevir; LDV, ledipasvir; OAE, overall adverse events; HCV, hepatitis C virus; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; RVR, rapid viral response; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TVR, telaprevir; vRVR, very rapid viral response.

4.1.4 Flow diagram of the numbers of studies included and excluded at each stage

A total of 9,500 citations were identified through electronic database searches using the OVID platform. Of these, 8,990 were excluded during abstract screening, leaving 510 citations. At full text review, a further 418 citations were excluded; 157 for study design, 121 for outcomes, 39 for interventions, and 101 for other reasons. Therefore, a total of 92 citations were identified via electronic database searching for inclusion within the SLR.

The screening of EASL and AASLD conference proceedings identified 66 abstracts (38 from EASL and 28 from AASLD). Of these, 11 were found to include data not already captured in the main search (4 from EASL and 7 from AASLD). Hand searching of included bibliographic reference lists, labels of included interventions, and clinical trial registries identified a further 7 relevant publications, of which 2 were conference abstracts. Finally, 10 clinical study reports (CSR) from trials sponsored by MSD were included. This gave a total of 50 included citations, relating to 40 clinical trials eligible for the inclusion into the NMA, of which 15 citations representing 8 clinical trials were included for EBR/GZR.

The flow of study selection is presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart in Figure 1.

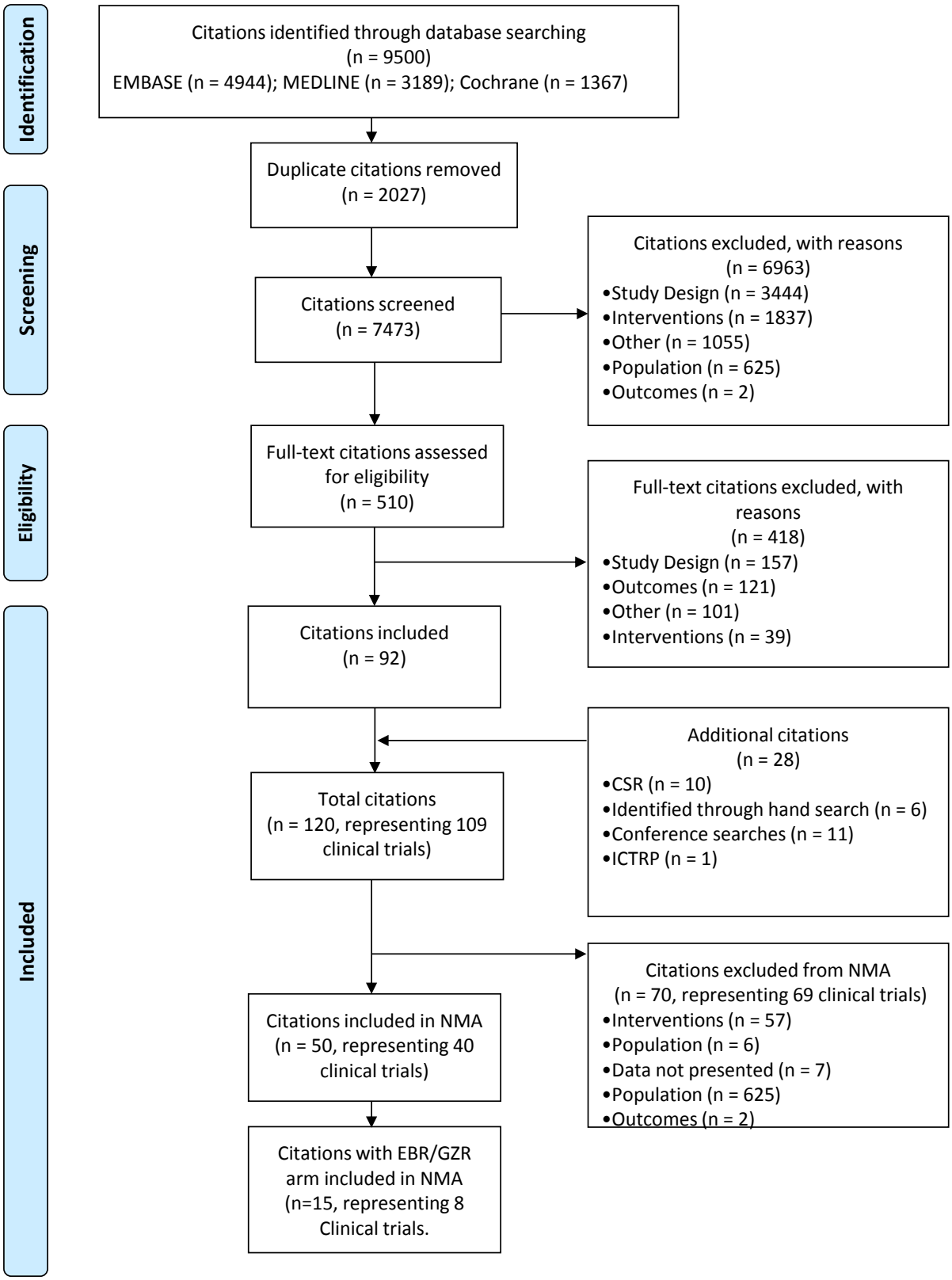
4.1.5 Single study data drawn from multiple sources

Data for each included EBR/GZR trial was provided by MSD via CSR if available. In addition, C-WORTHY was also reported in two publications (Lawitz et al. 2015 [52], Sulkowski et al. 2015[53]), and an additional publication was available for: C-SURFER (Roth et al. 2015[54]), C-EDGE CO-INFECTION (Rockstroh et al. 2015[55]), C-EDGE TN (Zeuzem et al. 2015[56]), C-EDGE TE (Kwo et al. 2015[57]), and C-EDGE CO-STAR (Dore et al. 2015[58]).

4.1.6 Complete reference list for excluded studies

A complete list for excluded studies (n=488) has been provided in Appendix 3.

Figure 1. PRISMA flow chart of included studies



Abbreviations. CSR, clinical study report; EBR/GZR, grazoprevir/elbasvir; ICTRP, international clinical trial registry platform; NMA, network meta-analysis. Note that 3 trials (5 citations) excluded for EBR/GZR relate to C-SALVAGE, C-SWIFT, and C-SALT, as described in section 4.2.2

4.2 *List of relevant randomised controlled trials*

4.2.1 List of relevant RCTs involving the intervention of interest

Summarised below are the seven relevant RCTs reporting treatment regimens of EBR/GZR 12 weeks, irrespective of cirrhosis stage and treatment experience. Of note, within the included trials there are treatment arms that are not relevant to the scope of this submission and are not considered further. A table summarising treatment arms excluded from the included trials this submission are reported in Appendix 4.

Table 21. Trials for EBR/GZR relevant to the NICE decision problem

Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
CSR MSD April 2015[59] Zeuzem et al. 2015 [56]	**C-EDGE TN** NCT02105467 PN060	Phase III Randomised, double blind, parallel group trial	TN; GT1a, 1b, and 4; cirrhotic and non-cirrhotic patients	EBR/GZR	Placebo
CSR MSD UK May 2015[60] Kwo et al. 2015 [57]	**C-EDGE TE** NCT02105701 PN068	Phase III Randomised, double blind, parallel group trial	TE; GT1a, 1b, and 4; cirrhotic and non-cirrhotic patients (MSD has considered only treatment arm 1 for EBR/GZR 12 weeks)	EBR/GZR	NA
CSR MSD UK April 2015 [14] Roth et al. 2015 [54]	**C-SURFER** NCT02092350 PN052	Phase II/III Randomised, blinded, parallel group trial	TN; GT1a and 1b; cirrhotic and non-cirrhotic patients described as IFN intolerant	EBR/GZR	Placebo
CSR MSD UK April 2015[61] Lawitz et al. 2015 [52], Sulkowski et al. 2015 [53]	**C-WORTHY** NCT01717326 PN035	Phase II Randomised, double blind trial	TN and TE; GT1a, 1b, and 4; cirrhotic and non-cirrhotic patients (MSD has considered only treatment arms: (A3, B3, B9, and B13)	EBR/GZR	NA
CSR MSD UK April 2015[62]	**C-SCAPE** NCT01932762 PN047.	Phase II Open label, randomised trial	TN: GT4, non-cirrhotic patients	EBR/GZR	NA

Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
CSR MSD UK Nov 2015[63] Dore et al. 2015 [58]	**C-EDGE CO-STAR** NCT02105688 PN062	Phase III Randomised, double blind, parallel group trial	TN; GT1a, 1b, and 4; cirrhotic and non-cirrhotic patients	EBR/GZR	Placebo
CSR MSD UK April 2016 [64]	**C-EDGE H2H** NCT02358044 PN077	Phase III Open label, randomised trial	TN, TE (prior PR treatment failures); GT1 (~60% GT1b) 4, and 6; cirrhotic (~25%) and non-cirrhotic patients	EBR/GZR	SOF+PR 12 weeks

Abbreviations. CSR, clinical study report; EMA, European Medicines Agency; EBR/GZR, grazoprevir/elbasvir; PR, Pegylated interferon and ribavirin; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naive

4.2.2 RCTs excluded from further discussion

Summarised below are trials that report EBR/GZR, and have been excluded from this submission.

Table 22 Studies excluded from the decision problem

Study details, phase	Population	Intervention*	Rationale for exclusion from decision problem
C-SALVAGE [65] NCT02105454 PN048 Phase II	Patients with chronic HCV GT1 infection who had previously failed on DAA therapy (BOC, TVR, SMV, or SOF) taken concomitantly with PR.	• EBR/GZR+RBV 12 weeks	The treatment regimen considered EBR/GZR in combination with RBV for 12 weeks; this does not support the EMA license or this submission.
C-SALT[66] NCT02115321 PN059 Phase II/III	Patients with chronic HCV GT1 infection described as either TN or TE with advanced cirrhosis and child Pugh B hepatic insufficiency.	**Part A** • EBR 50mg/GZR 50m/12 weeks • EBR 50mg/GZR 50m/12 weeks **Part B** • EBR 50mg/GZR 50mg or 100mg based on part A. **Part C** • EBR 50mg/GZR 50mg or 100mg based on part A or B.	The initial dose finding aspect of this study was designed to assess the optimal dose of EBR/GZR in patients with chronic HCV Child Pugh B hepatic insufficiency. This is not a specific subgroup of interest as per the EMA license. The primary endpoint of this study has not been assessed. Dose finding results of part A are not available for the treatment dose and treatment duration of interest, as per the EMA license.
C-SWIFT[67] NCT02133131 PN074 Phase II	Patients with chronic HCV infection GT1, and GT3, previously untreated (TN) with compensated cirrhosis or without cirrhosis.	• EBR 50mg/GZR 100mg+SOF 400mg 4 weeks; NC patients • EBR 50mg/GZR 100mg+SOF 400mg 6 weeks; NC or C patients • EBR 50mg/GZR 100mg+SOF 400mg 8 weeks; C patients Not relevant to this submission, GT3-EBR 50mg/GZR 100mg+SOF 400mg.	Data presented for GT1 infection reflect a treatment regimen/duration (4, 6, and 8 weeks), which does not reflect the anticipated EMA license or this submission. Data reported for patients with GT3 are not relevant to the EMA license or this submission.
C-EDGE InhBD PN065	Patients with chronic HCV GT1, 4, 6, previously untreated	• EBR 50mg/GZR 100mg 12 weeks • Matched placebo 12 weeks (deferred treatment EBR 50mg/GZR 100mg, 12	Data is not currently available to the sponsor As per clinical trials.gov the study completion data is estimated to

Study details, phase	Population	Intervention*	Rationale for exclusion from decision problem
NCT02252016 Phase III	(TN) with or without cirrhosis.	weeks)	be July 2016. The CSR has not been finalised and not anticipated to occur until [redacted] **This study is not included in the PRISMA flow chart, as status of CSR was known by MSD**
C-CORAL PN067 NCT02251990 Phase III	Patients with chronic HCV GT1, 4, or 6 infections, previously untreated (TN) with or without cirrhosis	• EBR 50mg/GZR 100mg 12 weeks • Matched placebo 12 weeks (deferred treatment EBR 50mg/GZR 100mg, 12 weeks)	C-CORAL has been designed and implemented to support licensing in Asia. This trial will enroll Asian patients only, with site study location listed as China, as listed on clinicaltrials.gov This trial is also listed as ongoing with data unavailable to the sponsor as of the 13th April 2016 **This study is not included in the PRISMA flow chart, as status of CSR was known by MSD**

Abbreviations. C, cirrhotic; EMA, European medicines agency; GT, genotype; EBR/GZR, grazoprevir/elbasvir; HCV, hepatitis C; NC, non-cirrhotic; SOF, sofosbuvir; TN, treatment naïve

*Note that unless stated the dose of EBR/GZR reported is GZR 100mg/EBR 50mg

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

4.3.1 Key aspects of listed RCTs

As described in section 1.1, EBR/GZR is awaiting a license from the EMA for the treatment of patients with HCV GT1a, GT1b, and GT4 infections irrespective of cirrhosis stage or treatment experience. To present a succinct overview of the clinical trial program, MSD has reported all aspects of the included trial methodologies below.

For each trial only the primary outcome SVR12 and the safety and tolerability of EBR/GZR has been reported (section 4.7). In section 4.3.2 all trial objectives have been reported for completeness. Data specifically relating to HRQoL is reported in section 5.4.1. The rationale for this is that MSD has presented the results of a post-hoc analysis specific to GT1a, GT1b, and GT4 split according to cirrhotic or non-cirrhotic status, and treatment experience. This approach facilitates the use of NMA and allows for comparisons according to DAA technologies recently recommended by NICE. It is these post-hoc analysis data that will inform the NMA reported in section 4.10, and the subsequent health economic analysis section 5.

C-EDGE TN Study, NCT02105467[56, 59]

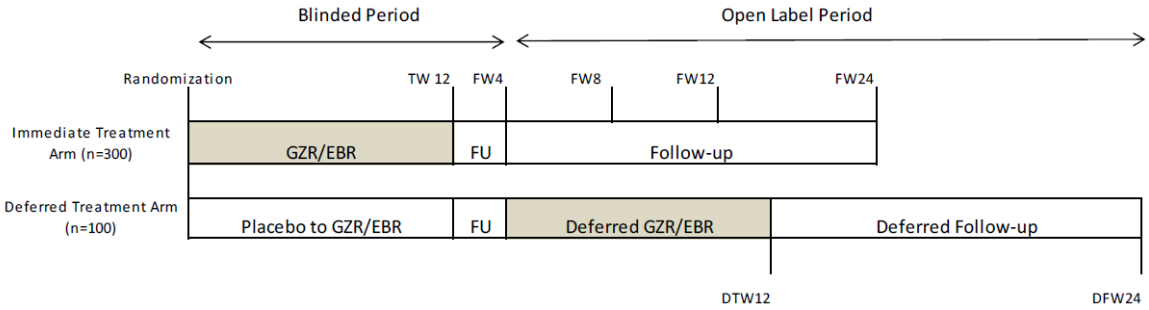
Trial design

C-EDGE TN is: a phase III, international, randomised double blind, placebo-controlled, parallel-group study that evaluated the efficacy and safety of EBR (50mg)/GZR (100mg) for 12 weeks treatment. C-EDGE TN enrolled 421 patients with a diagnosis of chronic HCV GT1 (1a, 1b), GT4, or GT6 described as treatment naïve cirrhotic or non-cirrhotic. Enrollment was managed to ensure that at least 20% of patients had compensated cirrhosis and that approximately 15% of patients had GT4 or GT6 infection. Only data for patients with GT1 and GT4 infections is considered.

Patients were randomised in a ratio of 3:1 using a central voice interactive response system (VIRS), according to a computer generated random allocation schedule to receive immediate or deferred treatment (Figure 2). Patients were stratified according to the presence or absence of cirrhosis and HCV genotype/sub-type. To ensure masking was preserved, both EBR/GZR and placebo were packaged identically. The patient, investigator, and sponsor personnel involved in the treatment or clinical evaluation of patients was unaware of the group assignments. However, an in-house un-blinded medical-monitoring team had access to the treatment group assignments to assist with safety and virological failures during the blinded phase of the study.

Patients were randomised to receive EBR (50mg)/GZR (100mg) once daily immediately (n=316) or placebo (n=105) (deferred treatment group) for 12 weeks. Patients in the immediate treatment group were treated for 12 weeks, with a follow-up of 24 weeks. Patients in the deferred treatment group were treated with placebo for 12 weeks, followed by a 4 week follow-up period and then 12 weeks of open-label treatment with EBR/GZR once daily, with a follow-up of 24 weeks after dosing was complete (Figure 2).

Figure 2. C-EDGE TN trial design[59]



TW = Treatment Week; FW = Follow-up Week; DTW = Deferred Treatment Week; DFW = Deferred Follow-up Week
GZB/EBR = Grazoprevir/Elbasvir; FU = Follow-up

Eligibility criteria

To be considered for inclusion into the C-EDGE TN trial, male and female patients had to have a diagnosis of HCV GT1, 4, or 6 (cirrhotic or non-cirrhotic) and be at least 18 years of age. In addition, patients had to satisfy the full list of inclusion/exclusion criteria listed in Appendix 5; key criteria have been summarised in Table 23 below.

Setting and location of data collection

C-EDGE TN was conducted in 60 centers across 10 countries including; Australia, Czech Republic, France, Germany, Israel, Puerto Rico, South Korea, Sweden, Taiwan, and the United Sates.

Trial drugs and concomitant medication

Patients were given either EBR/GZR or placebo as a FDC tablet once daily for 12 weeks at approximately the same time each day without regard for food. However, the intake of grapefruit or grapefruit juice during the dosing period was prohibited. If a dose was missed, and it was less than eight hours before the next dose, the patient was allowed to skip the missed dose and resume the normal dosing schedule; patients were instructed not to double the next dose to compensate for what had been missed.

To minimise the risk of drug-drug interactions every effort was made to limit the number of concomitant medications, and drugs known to be hepatotoxic were to be avoided during the

dosing period. A list of allowed and disallowed concomitant medication is reported in Appendix 5; this includes but is not limited to isoniazid, nitrofurantoin, St. John's Wort, organic anion-transporting polypeptide (OATP) inhibitors, HIV medicines and HMG-CoA reductase inhibitors (statins).

Primary outcome

To evaluate the efficacy of EBR/GZR as assessed by the proportion of patients in the immediate treatment group achieving SVR12, defined as HCV RNA <lower limit of quantification (LLoQ) 12 weeks after the end of all study therapy. To assess SVR (HCV RNA concentrations) blood samples were taken at baseline (screening), treatment day 1, weeks; 1, 2, 4, 6, 8, 10, and 12, and follow-up at the end of treatment at weeks 4, 8, 12, and 24. Hepatitis C RNA concentrations were measured using COBAS AmpliPrep/COBAS Taqman HCV test v2.0 (Roche Molecular Diagnostics, Branchburg, NJ) with a LLoQ of less than 15 IU/mL.

To evaluate the safety and tolerability of EBR/GZR using the immediate treatment group relative to the placebo (deferred) treatment group. The analysis of safety followed a tiered approach. Tier 1 safety events describe AEs of elevated laboratory values, and were recorded using p-values and 95% CI for between-treatment differences. Tier 2 safety included but was not limited to; any AE, any serious AE, any drug related AE, any serious AE related to study drug, and discontinuation related to AE (with an incidence of ≥4 patients in at least one treatment group). Tier 3 included safety events were reported if the frequency was <4 patients in both treatment groups. Safety and tolerability assessments (including: concomitant medication review, serious AE's, laboratory safety evaluations), were conducted at baseline, weeks; 1, 2, 4, 6, 8, 10, and 12 during therapy for the immediate treatment group, and weeks 16, 17, 18, 20, 22, 24, 26, and 28 for the deferred treatment group. Monitoring continued during the follow-up period at weeks 4, 8, 12, 16, 20, and 24. It is of note that safety data at 24 weeks follow-up was not available in the current CSR.

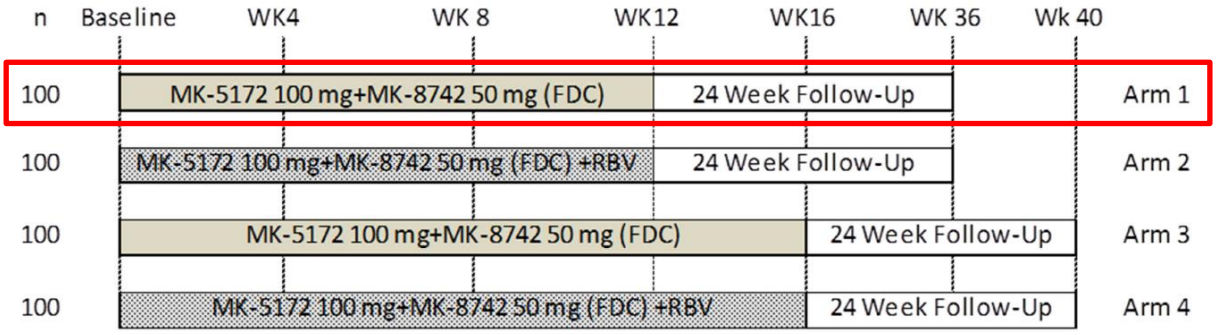
C-EDGE TE Study NCT02105701[60]

Trial design

C-EDGE TE is a phase III, randomised, parallel group, open-label, multisite trial of EBR (50mg)/GZR (100mg) administered once daily with or without RBV (twice daily) for 12 or 16 weeks in patients with chronic HCV GT1, GT4, or GT6 infection who had previously failed therapy with PR. The study was designed to enroll patients with cirrhosis (~30%), HIV co-infection (up to 20%), and not more than ~20% were to be PR relapsers. This was an open-label trial with respect to the treatments administered to patients. Data relating to treatment regimens of either 16 weeks or the inclusion of RBV have not been reported.

Patients were randomised in a 1:1:1:1 ratio to receive 12 weeks of treatment with EBR/GZR once daily, 12 weeks of treatment with EBR/GZR once daily+RBV twice daily, 16 weeks of treatment with EBR/GZR once daily, or 16 weeks of EBR/GZR once daily+RBV twice daily (Figure 3). Randomisation was performed using a VIRS stratified according to cirrhosis (yes or no) and prior PR treatment response (relapser, partial responder, or null responder).

Figure 3. C-EDGE TE – Trial design[60]



Abbreviations. FDC, fixed dose combination; MK5173/8742, grazoprevir/elbasvir; RBV, ribavirin; WK, week

Eligibility criteria

Patients had to satisfy a number of inclusion and exclusion criteria, this included but was not limited to: patients aged at least 18 years of age; a diagnosis of HCV GT1, GT4, or GT6 infection (with no evidence of non-typeable or mixed genotype infection); a baseline viral load of ≥10,000IU/mL in peripheral blood at screening; cirrhosis staging confirmed by either liver biopsy, Fibroscan, or FibroSure, and previous HCV treatment with PR defined as null-responder, partial-responder, or treatment relapser. A complete list of inclusion/exclusion criteria are listed in Appendix 5; and have been further summarised in Table 23.

Setting and location of data collection

C-EDGE TE was conducted in 65 study centres across 15 countries including; Australia, Canada, Denmark, Finland, France, Israel, Korea, Malaysia, Netherlands, New Zealand, Poland, Puerto Rico, Spain, Taiwan, and the USA.

Trial drugs and concomitant medication

A total of 420 patients were randomly assigned to:

- EBR (50mg)/GZR (100mg) 12 weeks (n=105)
- EBR (50mg)/GZR (100mg)+RBV, 12 weeks (n=104)
- EBR (50mg)/GZR (100mg) 16 weeks (n=105)
- EBR (50mg)/GZR (100mg)+RBV 16 weeks (n=106)

Patients took EBR/GZR as a single fixed dose combination tablet once daily (at approximately the same time each day) for 12 or 16 weeks with or without RBV twice daily

(weight-based dosing regimen/200mg; total daily dose 800-1,400mg/day); patients were advised that RBV must be taken with food. The initial dose was taken at the trial site on day 1; all subsequent dosing occurred at a patient's home and was unsupervised.

A number of contraindicated medications and vaccines were described; this included but was not limited to hepatotoxic drugs, strong and moderate cytochrome P450 inducers, OATP inhibitors, named HIV medications, proton pump inhibitors, and herbal supplements. Allowed medicines included; anticoagulants, antihypertensives, erythropoietin, diuretics, statins, hypoglycemic agents, and anti-depressants. A full list of allowed and disallowed concomitant medication is reported in Appendix 5.

Primary outcomes

To evaluate the efficacy of EBR/GZR assessed by the proportion of patients in each treatment group achieving SVR12; this was defined as HCV RNA <LLoQ 12 weeks after the end of all study therapy. To assess SVR (HCV RNA concentrations) blood samples were taken at screening, baseline, treatment weeks 2, 4, 6, 8, 10, 12 (weeks 14 and16 for prolonged treatment group), and follow up after study completion at weeks 4, 8, 12, and 24. HCV RNA concentrations were measured using Roche COBAS Ampliprep/COBAS Taqman HCV test v2.0 with a lower limit of quantification (LLoQ) of ≥15 IU/mL.

To evaluate the safety and tolerability of EBR/GZR with or without RBV as assessed by clinical evaluation of AEs and inspection of other study parameters including vital signs, physical examinations, 12-lead ECGs, standard laboratory tests, as well as HIV RNA and CD4 cell counts (for co-infected patients) were conducted as per the trial flow chart at various time points. A review of AE/SAE was conducted in line with HCV RNA assessment timings as described above.

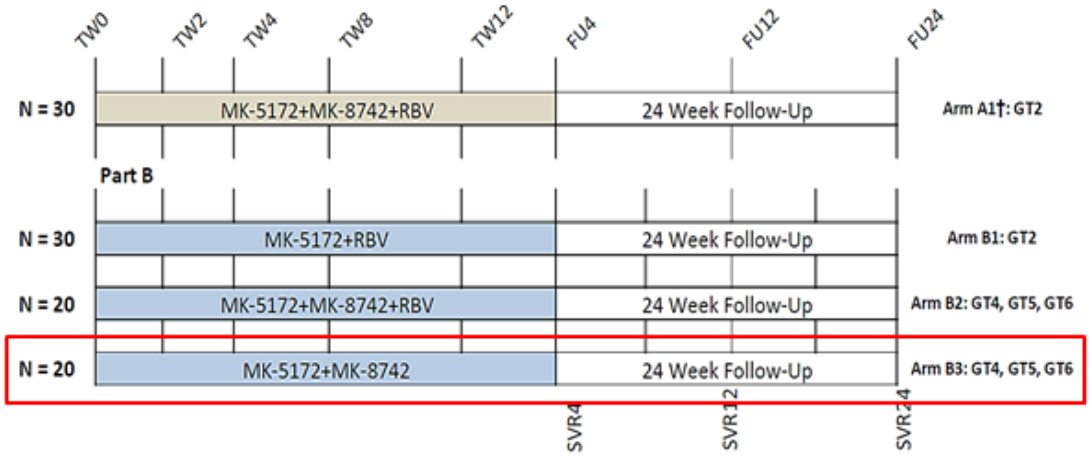
C-SCAPE Study NCT01932762[62]

Trial design

C-SCAPE is a phase 2, randomised, open-label, parallel-group trial multicenter trial of EBR (50mg)/GZR (100mg) administered once daily for 12 weeks with or without RBV in patients described TN, NC with GT4, 5, or 6 infections. This study planned to enroll ~20 patients into arm B3 (arm of interest), and was managed to ensure a minimum of 4 patients with GT4 or GT6.

Patients were randomised in a 1:1 ratio, stratified by genotype, using a VIRS into either treatment arm B2 (EBR (50mg)/GZR (100mg)+RBV) or B3 (EBR (50mg)/GZR (100mg)). Treatment was administered for 12 weeks in both treatment arms, and patients in both arms were followed for 24 weeks after the cessation of study therapy (Figure 4). This was an open-label trial; therefore the sponsor, investigator, and patients knew the treatment administered.

Figure 4. C-SCAPE trial design[62]



† Arms were identified slightly differently in P047 Protocol (in the protocol Arm A1 was Arm 1; Arm B1 was Arm 2; Arm B2 was Arm 3; and Arm B3 was Arm 4).

Eligibility criteria

To be considered for inclusion patients had to have a diagnoses of chronic HCV infection (GT4, GT5, or GT6) and be TN. Additional criteria included, but were not limited to; age ≥18 years, body weight of ≥50kg and ≤25kg, a positive HCV antibody test with a screening HCV RNA ≥10,000 IU/mL in peripheral blood, and absence of cirrhosis. The full list of inclusion/exclusion criteria listed in Appendix 5.

Setting and location of data collection

C-SCAPE was conducted in 30 study centres across 7 countries including; United states, Australia, Israel, France, UK, Spain, and Belgium. Note that 3 study centres were included within the UK.

Trial drugs and concomitant medication

A total of 98 patients were assigned to four treatment groups:

- Arm A1; EBR (50mg)/GZR (100mg)+RBV, 12 weeks (n=30)
- Arm B1; GZR (100mg)+RBV 12 weeks (n=30)
- Arm B2; EBR (50mg)/GZR (100mg)+RBV, 12 weeks (n=19)
- Arm B3; EBR (50mg)/GZR (100mg), 12 weeks (n=19)

Patients included in trial arm B2 and B3 were randomised. Only treatment arm B3 is of relevance to this submission, enrolling patients with; HCV GT4 infection irrespective of cirrhosis state and who were TN.

Patients took EBR/GZR as a single FDC once daily (at approximately the same time each day) for 12 weeks without RBV. The initial dose was taken at the trial site on day one and at a subject's home thereafter. If a patient missed EBR/GZR and less than 8 hours remained before the next dose of study therapy, then the missed dose was to be skipped, and a normal schedule resumed.

A number of contraindicated medications were described; this included but was not limited to: strong CYP3A/P-gp inhibitors, strong and moderate CYP3A/P-gp inducers, OATP inhibitors, all HMG-CoA reductase inhibitors (statins), and drugs classes such as proton pump inhibitors, H2 antagonists, and other anti-ulcer agents (gastric acid suppressants). A full list of included/excluded medicines is reported in the Appendix 5.

Primary outcomes

To evaluate the efficacy of EBR/GZR as assessed by the proportion of patients in each treatment group achieving SVR12; this was defined as HCV RNA <LLoQ 12 weeks after the end of all study therapy (Table 23). To assess SVR (HCV RNA concentrations) blood samples were taken at screening, day 1 and 7 of treatment week 1, treatment weeks 2, 4, 8, and 12, and follow up after study completion at weeks 4, 12, and, 24. HCV RNA concentrations were measured using Roche COBAS Ampliprep/COBAS Taqman HCV test v2.0 with a lower limit of quantification (LLoQ) of ≥25 IU/mL.

To evaluate the safety and tolerability of EBR/GZR a number of parameters were assessed, including: vital signs, physical examinations, 12-lead ECG, and standard laboratory safety

tests. An adverse event was defined as any unfavorable and unintended sign symptom or disease temporarily associated with the use of a medicinal product or protocol specified procedure, whether or not considered to be related to the medicinal product or protocol specified procedure. Any worsening of a pre-existing condition that is temporarily associated with the use of the product is also an adverse event. A SAE was described as any adverse experience that: results in death, is life threatening, result in persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalisation, or is a congenital anomaly/birth defect.

C-EDGE CO-STAR Study NCT02105688[63]

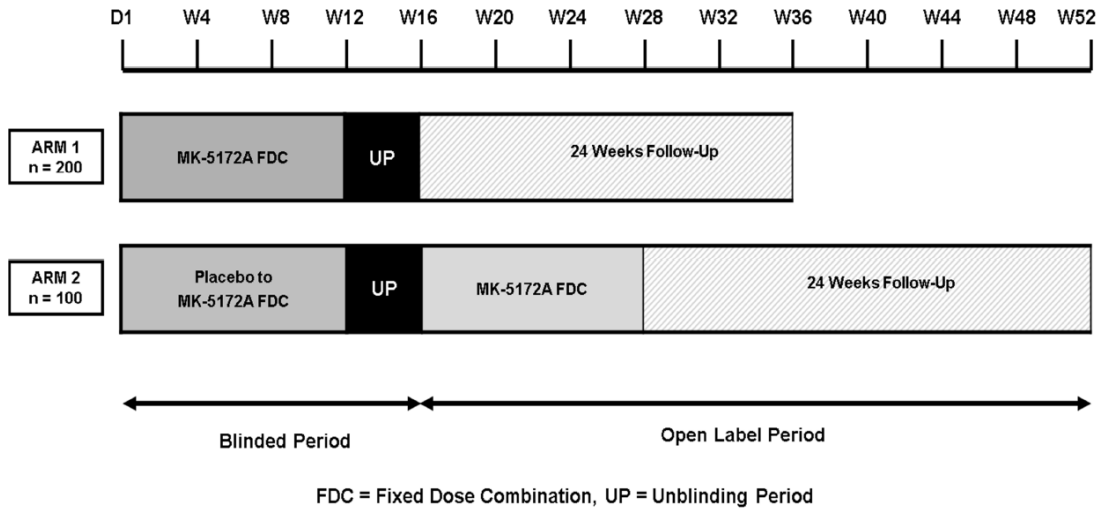
Trial design

C-COSTAR is a phase III, randomised, parallel group, double blind, placebo controlled, multisite trial of EBR (50mg)/GZR (100mg) administered once daily for 12 weeks in TN, cirrhotic or non-cirrhotic patients with HCV GT1, GT4, or GT6 infections, and who were also in receipt of OST. This study was designed to enroll ~300 patients; and was managed to allow ~20% of patients with evidence of compensated cirrhosis.

Patients were randomised in a 2:1 ratio using a VIRS into either the immediate EBR/GZR or deferred (placebo to EBR/GZR) treatment groups. To ensure masking was preserved, both EBR/GZR and placebo were manufactured to look visually identical and were packaged identically. Patients, the investigator, and the sponsor personnel involved in the treatment or clinical evaluation of patients were unaware of the treatment group assignments; this was maintained through to week 16 of the study. However, an in-house un-blinded medical team had access to treatment assignments and HCV RNA results. These personnel were responsible for the monitoring of virological failures, and a review of SAEs “as needed” during the blinded phase of the study.

Patients were randomised to receive EBR (50mg)/GZR (100mg) FDC once daily immediately (n=201) or placebo (n=100) (deferred treatment group) for 12 weeks (Figure 5). At the end of 12 weeks, patients in both treatment groups were un-blinded, and the placebo group underwent a 4-week washout period followed by 12 weeks of active open-label treatment with EBR (50mg)/GZR (100mg) once daily (Figure 5). Patients in both treatment arms were followed for 24 weeks at the end of active therapy.

Figure 5. C-COSTAR trial design[63]



Eligibility criteria

To be considered for inclusion patients had to have a diagnosis of chronic HCV infection (GT1, GT4, or GT6), be TN, and be on OST. Additional criteria included, but were not limited to; age ≥18 years and a positive HCV antibody test with a screening HCV RNA ≥10,000 IU/mL in peripheral blood. Patients were not excluded based on cirrhosis stage. The full list of inclusion/exclusion criteria is in Appendix 5, and a tabulated summary is provided below in Table 23.

Setting and location of data collection

C-EDGE CO-STAR was conducted in 55 centres in 14 countries including; USA, UK, Spain, Australia, Canada, France, Romania, Taiwan, Germany, Norway, Puerto Rico, New Zealand, Netherlands, and Israel. Of note, the UK included 6 study centres.

Trial drugs and concomitant medication

Patients received placebo or GZR (100mg)/EBR (50mg) as a single FDC tablet once daily for 12 weeks at approximately the same time without regard for food. However, the intake of grapefruit or grapefruit juice during the dosing period was prohibited. Investigators reviewed prescription and non-prescription medications before starting the study and at each study visit. A number of medications were prohibited; these included but were not limited to: known hepatotoxic drugs (etofoxine, isoniazid), herbal supplements, and strong and moderate CYP3A/P-gp inhibitors (rifampin, anticonvulsants, St. John's Wort etc.) A full list of allowed and disallowed concomitant medication is reported in the Appendix 5.

Primary outcomes

To evaluate the efficacy of EBR/GZR as assessed by the proportion of patients in each treatment group achieving SVR12; this was defined as HCV RNA <LLoQ 12 weeks after the end of all study therapy. To assess SVR (HCV RNA concentrations) in the immediate treatment group, blood samples were taken at screening, days 1 and 7 of the first week, weeks 2, 4, 6, 8, 10, and 12 of blinded treatment, and follow-up weeks 4, 8, 12, and 24. Similarly, the deferred treatment group (placebo) was monitored as per the timings described above during blinded treatment. HCV RNA concentrations, for the deferred treatment group during open-label therapy, were assessed at weeks 16, 17, 18, 20, 22, 24, 26, and 28, and at follow-up weeks as described for the immediate treatment group. HCV RNA levels in the plasma were measured using the Roche COBAS Ampliprep/COBAS Taqman HCV test v2.0 with a LLoQ of <15 IU/mL.

To evaluate the safety and tolerability of EBR/GZR in the immediate treatment group relative to the deferred treatment group (placebo). Adverse events were assessed using a number of parameters including vital signs, physical examinations, 12-lead ECG, standard laboratory safety tests, as well as HIV RNA and CD4 cell counts. An AE was defined as; any unfavorable and unintended sign symptom or disease temporally associated with the use of a medicinal product or protocol specified procedure, whether or not considered to be related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that is temporally associated with the use of the product is also an adverse event.

C-SURFER Study NCT02092350[14]

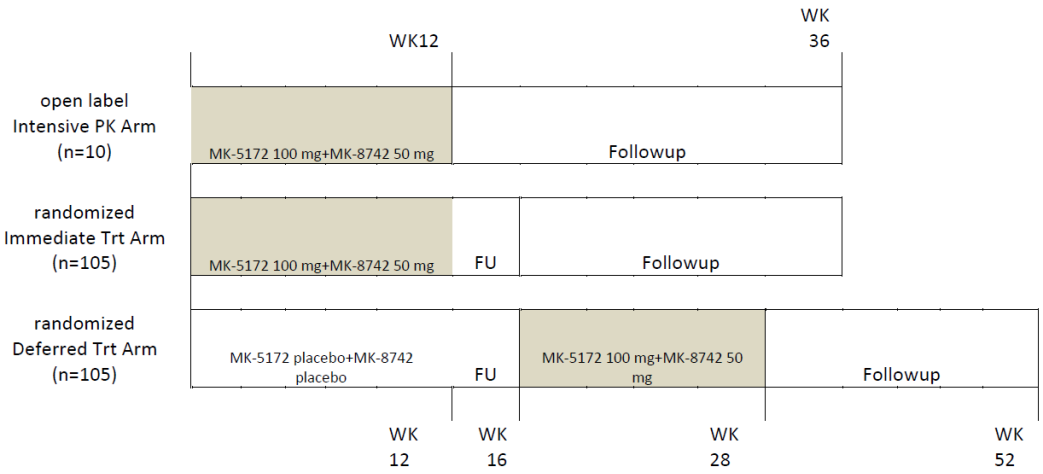
Trial design

C-SURFER is a phase III, double blind, multisite, placebo-controlled trial, which comprised of a randomised study of efficacy and safety, and an observational (PK group) study of efficacy. C-SURFER enrolled 224 patients with CKD stage 4 or 5 with HCV GT1 infection described as either TN or TE (patients had previously received an IFN-regimen). Chronic kidney disease stages 4 and 5 were based on an eGFR of 15–29 mL/min per 1.73 m^2 and less than 15 mL/min per 1.73 m^2 or, on dialysis, respectively. C-SURFER represents a population with significant unmet clinical need. Note that the primary outcome was reported for both the immediate (randomised arm) and observation arm combined.

Patients were randomised in a 1:1 ratio using a VIRS stratified according to dialysis (yes/no) and the presence of diabetes (yes/no) with a block size of 4. To ensure masking was preserved, both EBR/GZR and placebo were manufactured to look visually identical and were packaged identically. Patients and site personnel were masked to treatment assignment. Patients were randomised to receive EBR (50mg)/GZR (100mg) once daily

immediately (n=111) or placebo (n=113) (deferred treatment group) for 12 weeks (Figure 6). At the end of 12 weeks patients from the placebo group underwent a 4 week washout period and started open-label treatment with EBR (50mg)/GZR (100mg) once daily for 12 weeks as the deferred treatment group; patients and site personnel were unmasked at the start of treatment for the deferred treatment group. In addition, an intensive PK open-label group (n=11) were enrolled to receive EBR (50mg)/GZR (100mg) once daily for 12 weeks.

Figure 6: C-SURFER – Trial design[14]



Abbreviations. FU, follow up; MK5172+MK8742, grazoprevir/elbasvir; PK, pharmacokinetic; Trt, treatment; WK, week. **Note.** This figure illustrates the number of patients planned for enrollment

Eligibility criteria

To be considered for inclusion patients had to have a diagnosis of chronic HCV GT1 (cirrhotic or non-cirrhotic) infection and CKD stage 4–5 (with or without haemodialysis dependence) renal impairment, and be at least 18 years of age. In addition, patients had to satisfy the full list of inclusion/exclusion criteria listed in Appendix 5; this is summarised in Table 23.

Setting and location of data collection

C-SURFER was conducted in 68 centers in 12 countries including; USA, Argentina, Australia, Canada, Estonia, France, Israel, South Korea, Lithuania, Netherlands, Spain, and Sweden.

Trial drugs and concomitant medication

A total of 226 patients were randomly assigned to the immediate treatment group, n=111 GZR (100mg)/EBR (50mg) for 12 weeks or matched placebo, n=113 (deferred group) EBR (50mg)/GZR (100mg). In addition, 11 patients were enrolled into an open-label intensive PK group and received EBR (50mg)/GZR (100mg) for 12 weeks. Patients took either placebo or

EBR/GZR as a single FDC tablet once daily for 12 weeks at approximately the same time without regard for food. However, the intake of grapefruit or grapefruit juice during the dosing period was prohibited. Drugs known to be hepatotoxic were to be avoided during the dosing period. A full list of allowed and disallowed concomitant medication is reported in Appendix 5.

Primary outcomes

To evaluate the efficacy of EBR/GZR as assessed by the pooled estimate of non-randomised PK population (n=11) and immediate treatment group (n=111) combined vs. the historical patient control group with a SVR12 rate of 45%. SVR12 was defined as HCV RNA <LLoQ 12 weeks after the end of all study therapy. To assess SVR (HCV RNA concentrations) blood samples were taken at baseline and treatment weeks 1, 2, 3, 4, 6, 8, 10, and 12, and at 4, 12, and 24 weeks after the end of treatment. Hepatitis C RNA concentrations were measured using Roche COBAS Ampliprep/COBAS Taqman HCV test v2.0 with a lower limit of quantification of <15 IU/mL. Patients undergoing haemodialysis had samples taken prior to dialysis.

To evaluate the safety and tolerability of EBR/GZR the immediate treatment group was compared with the deferred (placebo) treatment group. Adverse events were graded according to a standardised scale defined as: any unfavorable and unintended sign symptom, or disease temporarily associated with the use of a medicinal product or protocol specified procedure, whether or not considered to be related to the medicinal product or protocol specified procedure. Any worsening of a pre-existing condition that is temporarily associated with the use of the product is also an AE. Additional routine laboratory tests included electrocardiograms, and symptom-directed physical examinations at baseline, during, and after completion of treatment.

C-WORTHY Study NCT01717326[61]

Trial design

C-WORTHY is a phase II, randomised, multicenter, parallel-group trial that reported the efficacy, and safety/tolerability of EBR/GZR in patients diagnosed with chronic HCV GT(1) 1a, 1b, and 3 infections cirrhotic/non-cirrhotic. A total of 573 patients were enrolled and distributed across 20 treatment arms. Please see Figure 7 below for the trial design (A, B, C, and D). To support the anticipated EMA license and this submission only data reported for EBR (50mg)/GZR (100mg) for 12 weeks treatment will be considered.

Part A was a double blind, dose-response evaluation of EBR/GZR 12 week regimens without an active comparator in patients described as TN, NC with GT1 infection only. Patients were

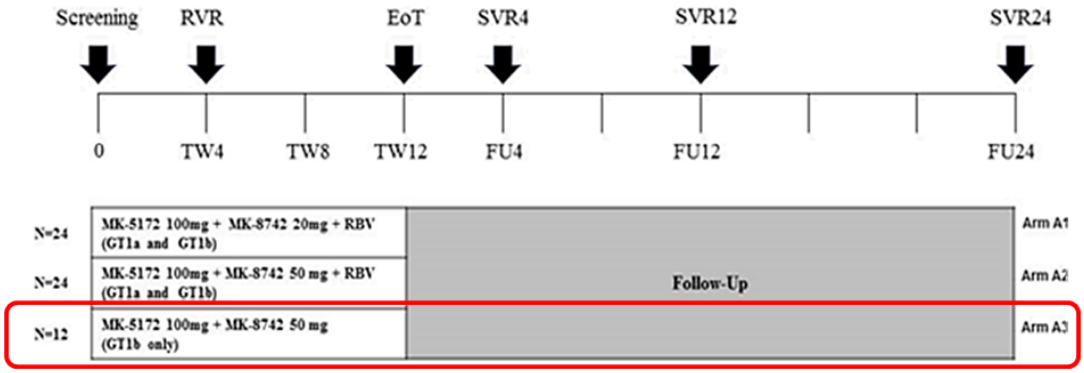
randomised in a 1:1:1 ratio to one of the three treatment arms for GT1b, and in a 1:1 ratio to treatment arms A1 and A2 for GT1a (GT1a infection was to account for at least 50% of the included patients). The three treatment arms considered in part A reported a varying dose of EBR (20mg or 50mg) in combination with GZR (100mg) +/- RBV. The patients and investigators were blinded to treatment group assignment. However, for the RBV free arm A3 (arm of interest), the EBR/GZR dose was not blinded.

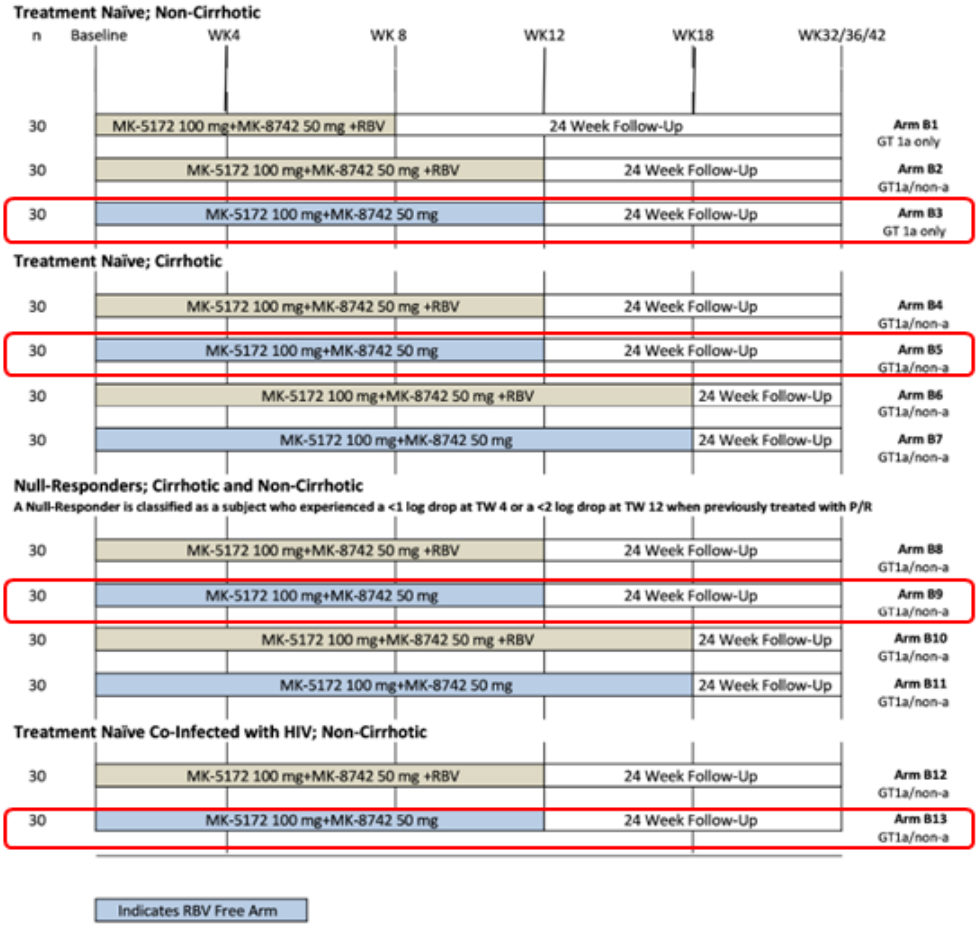
Part B evaluated 8, 12, or 18 weeks of open-label treatment of EBR (50mg)/GZR (100mg) +/- RBV in patients with or without cirrhosis, TN or TE prior null response, or who were co-infected with HIV. Patients were randomised to one of 13 treatment arms (except for arms B12 and B13); both the patient and investigator were blinded to the duration of treatment. For parts A and B randomisation was performed centrally using an VIRS.

The relevant treatment arms include:

- Treatment arm A3: TN, NC, GT1b infection only, (n=13)
- Treatment arm B3: TN, NC, GT1a infection only (n=31)
- Treatment arm B5: TN, C, GT1a and 1b infections (n=29)
- Treatment arm B9: TN or TE, C or NC, GT1a and 1b infections (n=33)
- Treatment arm B13: HIV co-infected, TN, NC, GT1a and 1b infection (n=30).

Figure 7 Trial design – C-WORTHY[61]





Abbreviations. GT, genotype; MK5172/8742, grazoprevir/elbasvir; RBV, ribavirin; WL, week **Note**. Only those treatment arms are considered relevant to decision problem

Eligibility criteria

The inclusion criteria for C-WORTHY varied according to study part A, B, C, and D and have been summarised in Table 23, full details are reported in Appendix 5. A number of considerations were required irrespective of study part, this included but was not limited to: patients aged ≥18 years, presence of chronic compensated HCV genotype: GT1 infection (Part A, Part B), a baseline HCV RNA level of ≥10,000 IU/mL in peripheral blood, and liver disease stage assessment using one of the methods described in the Appendix 5. Similarly, a number of exclusion criteria were reported, including but not limited to; mixed infections, HIV co-infected (Part A only), HBV co-infected, evidence of HCC, taking herbal supplements i.e. St John's Wart, pre-existing psychiatric disorders, and a range of co-morbid conditions; a full list of criteria split according to treatment parts A, B, C, and D is provided in Appendix 5.

Setting and location of data collection

C-WORTHY was conducted at 76 centers in 12 countries including; United States, Australia, Canada, Denmark, France, Hungary, Israel, New Zealand, Puerto Rico, Spain, Sweden, and Turkey.

Trial drugs and concomitant medication

A total of 573 patients were randomised in the C-WORTHY trial. Of these, 136 patients were randomly assigned to receive EBR (50mg)/GZR (100mg) for 12 weeks in the relevant treatment arms (A3, B3, B5, B9, and B13) described above. EBR/GZR was taken by patients once daily as a single FDC tablet for 12 weeks at approximately the same time each day without regard for food; however, the intake of grapefruit or grapefruit juice was contraindicated during the treatment period of the trial.

To minimise the risk of drug-drug interactions every effort was made to limit the number of concomitant medications. Contraindicated medications included, but was not limited to: strong CYP3A/P-gp inhibitors, strong and moderate CYP3A/P-gp inducers, OATP inhibitors, named HIV medications, all HMG-CoA reductase inhibitors (statins), herbal supplements, and a number of drug classes (i.e. proton pump inhibitors, systemic corticosteroids) (Table 23). A full list of concomitant medicines is reported in Appendix 5.

Primary outcome

To evaluate the efficacy of EBR/GZR reported as the proportion of patients achieving SVR12. To assess SVR rates HCV RNA concentrations were measured using the Roche COBAS Taqman HCV test v2 on blood samples taken from each patient at screening, baseline, and various time points throughout the study with a LLoQ of 25 IU/mL. For part A, patients were assessed at: screening, on days 1, 3, 5 and 7 during week 1, weeks 2-12, and follow up weeks 2, 4, 8, 12, and 24. For parts B, C, and D, patients were assessed at: screening, day 1 and 7 during week 1, weeks 2, 4, 7, 12, 16, and 18 (as relevant per treatment regimen), and follow up weeks 4, 8, 12, and 24.

To evaluate the safety and tolerability of EBR/GZR an assessment of adverse experiences and other study parameters including: vital signs, physical examinations, 12-lead ECGs and standard laboratory safety tests were carried out by clinical investigators. An AE was defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. The analysis of safety followed a tiered approach. Tier 1 safety events describe AEs of elevated laboratory values, and were recorded using p-values and 95% CI for between-treatment differences. Tier 2 safety included but was not limited to; any AE, any serious AE, any drug related AE, any serious AE related to study drug, and discontinuation related to AE (with an incidence of ≥4 patients in at least one treatment group). Tier 3 included safety events were reported if the frequency was <4 patients in both treatment groups.

For part A, the efficacy assessment for SAEs were conducted at screening, days 1,3, 5 and 7 during treatment week 1, treatment weeks 2-12, and at follow up weeks 2,4,8, 12 and 24. For parts B, C, and D efficacy assessment for SAE were conducted on days 1 and 7 during treatment week one, weeks 2, 4, 8, 12, 16, and 18 during treatment as relevant (treatment duration), and follow up weeks 4, 8, 12 and 24.

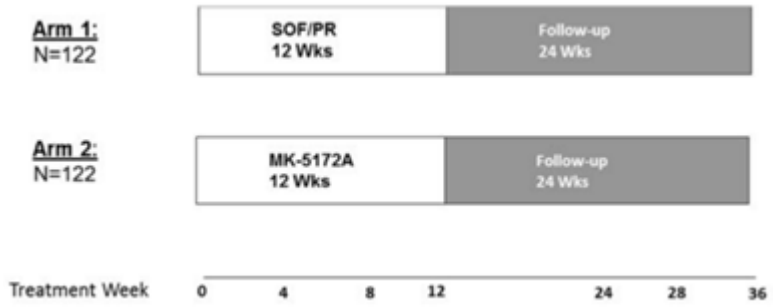
C-EDGE H2H Study NCT02358044[64]

Trial design

C-EDGE H2H is a phase III, randomised, multicenter, clinical trial designed to evaluate the efficacy, and safety and tolerability of EBR/GZR compared with the active control SOF+PR in patients diagnosed with chronic HCV GT(1) 1a, 1b, 4, and 6 infections. Patients were further described as either TN or TE (prior PR treatment failures), and were either cirrhotic or not. The study planned to enroll 122 patients per treatment arm (Figure 8).

Patients were randomised in a 1:1 ratio, using a VIRS/integrated web response system (centrally coordinated), to either the EBR/GZR or SOF+PR. Treatment was administered for 12 weeks in both treatment arms, and patients in both arms were followed up for 24 weeks after the cessation of study therapy (Figure 8). This was an open-label trial; therefore the sponsor, investigator, and patients knew the treatment administration.

Figure 8. Trial design – C-EDGE H2H[64]



Eligibility criteria

To be considered for inclusion patients had to be at least 18 years of age with a diagnosis of chronic HCV infection (GT1, GT4, or GT6), irrespective of cirrhosis status, and treatment experience (TE = failed prior treatment with PR, null responder, partial responder, relapser). Treatment experienced was defined as; 1) peg-IFN/RBV null responder <2log10 IU/mL reduction in HCV RNA at week 12, or <1 logIU/mL decline from baseline at week 4 and discontinued therapy prior to week 12; 2) peg-IFN/RBV partial responder >2log10 IU/mL reduction in HCV RNA by week 12 of treatment, but HCV RNA quantifiable (≥LLoQ) at the end of treatment; 3) prior peg-IFN/RBV relapser, patient relapsed after completing a prior

course of HCV therapy of a dual regimen of peg-IFN/RBV (HCV RNA undetectable at the end of treatment with peg-IFN containing regimen, but HCV RNA quantifiable (≥LLoQ)) during follow-up). Additional criteria included, but were not limited to; confirmed cirrhosis by an approved method listed in the protocol, and a positive HCV antibody test with a screening HCV RNA ≥10,000 IU/mL. A comprehensive list of inclusion/exclusion criteria is reported in Appendix 5.

Setting and location of data collection

C-EDGE H2H was conducted in 32 study centres across 9 countries including; Czech Republic, Denmark, Hungary, Lithuania, Norway, Poland, Romania, Spain, and Turkey.

Trial drugs and concomitant medication

Patients received either:

- EBR (50mg)/GZR (100mg) as a FDC tablet once daily for 12 weeks without regard for food. If a dose of EBR/GZR was missed, the missed dose was to be skipped and the normal schedule resumed. If the dosing schedule was interrupted for more than 3 days the sponsor was to be consulted.
- SOF (400mg) once daily + Peg-IFN 1.5mcg per Kg once weekly, and RBV 1000-1200mg twice daily for 12 weeks. SOF was taken without regard for food, and if a dose was missed this could be taken later in the same day; however, no more than 400mg of SOF could be taken on one calendar day and the patient would resume the regular schedule on the next day. Peg-IFN alpha 2b was administered by subcutaneous injection (Redipen®) based on individual weight. Patients were taught how to self-administer, and were advised to administer on the same day each week. If the patient realised that a dose had been missed, within four days of the scheduled dose, this was to be administered and patients were to resume a regular schedule (patients were not to “double-up” on a missed dose if it was outside the 4 day window). RBV was administered twice daily with food based on individual weight.

Patients received the initial dose of therapy at the trial site. Subsequent dosing was performed at approximately the same time each day; this was unsupervised at his or her home.

The study protocol outlined a number of concomitant medications that were not allowed during this trial. Deviations and potential discontinuation from the study were discussed with the sponsor, the investigator, and the subject. Excluded medication included; known hepatotoxic drugs, strong CYP3A/P-gp inducers, OATP inhibitors, and named HIV medications. A comprehensive list of excluded medication is reported in Appendix 5.

Primary outcomes

To evaluate the efficacy of EBR/GZR compared with SOF+PR, as assessed by the proportion of patients achieving SVR12 after the end of all study medication. SVR12 was defined as the HCV RNA >LLoQ 15IU/mL (target unquantifiable or target not detected) 12 weeks after the end of all study medication. This was assessed using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0. Patients were assessed during screening, day 1 and 7 of week 1, weeks 2, 4, 5, 8, 10 and 12 of treatment, and during follow-up weeks 4, 8, 12, 16, 20 and 24. In addition, the primary objective also assessed the safety and tolerability of EBR/GZR compared with SOF+PR.

4.3.2 Comparative summary of the methodology of the RCTs

Table 23. Comparative summary of trial methodology (1)

Criteria	C-EDGE TN[59] NCT02105467	C-EDGE TE[60] NCT02105701	C-SCAPE[62] NCT01932762	C-EDGE CO-STAR[63] NCT02105688
Study location	• 60 study centres • 10 counties; Australia, Czech Republic, France, Germany, Israel, Puerto Rico, South Korea, Sweden, Taiwan, and the United Sates	• 65 study centres • 15 countries; Australia, Canada, Denmark, Finland, France, Israel, Korea, Malaysia, Netherlands, New Zealand, Poland, Puerto Rico, Spain, Taiwan, and the USA	• 30 study centres • 7 countries; United states, Australia, Israel, France, UK, Spain, and Belgium	• 55 study centres • 14 countries; USA, UK, Spain, Australia, Canada, France, Romania, Taiwan, Germany, Norway, Puerto Rico, New Zealand, Netherlands, Israel
Trial design	• Phase III • Randomised, double blind controlled (patients, study investigator, and sponsor personnel blinded) • Cross over treatment arm	• Phase III • Randomised, open-label • Parallel group *Treatment arm A is of relevance to this submission*	• Phase II • Two part, open-label, parallel group, partially randomised (treatment arm B2 and B3 only)	• Phase III • Randomised, double blind immediate treatment group (placebo controlled) • Parallel group, cross over to open-label active therapy
Eligibility criteria	• Chronic HCV GT1, 4, or 6 • Treatment naïve patients • Cirrhotic or non-cirrhotic • Aged ≥18 years • HCV≥10,000IU/mL at screening	• Chronic HCV GT1, 4, or 6 • Treatment experienced, having failed prior PEG+RBV treatment • Cirrhotic or non-cirrhotic • Aged ≥18 years • HCV≥10,000IU/mL at screening	• Chronic HCV GT2, 4, 5, or 6 (Part B only) • Treatment naïve • Aged ≥18 years • HCV≥10,000IU/mL at screening	• Chronic HCV GT1, 4, or 6 • Treatment naïve • Cirrhotic or non-cirrhotic • Aged ≥18 years • HCV≥10,000IU/mL at screening • HIV HCV co-infected patients
Trial drugs (intervention, details for administration, posology)	Intervention • EBR(50mg)/GZR(100mg), FDC tablet 12 weeks, taken once daily without regard to food Comparator • Placebo	Intervention • EBR(50mg)/GZR(100mg), FDC tablet 12 weeks, taken once daily without regard to food Comparator • No active control	Intervention • Arm B3: EBR(50mg)/GZR(100mg), FDC tablet 12 weeks Comparator • No active control	Intervention • EBR(50mg)/GZR(100mg), FDC tablet 12 weeks Comparator • Placebo

Criteria	C-EDGE TN[59] NCT02105467	C-EDGE TE[60] NCT02105701	C-SCAPE[62] NCT01932762	C-EDGE CO-STAR[63] NCT02105688
Concomitant medication	Concomitant medication† • Disallowed medication; known hepatotoxic drugs, herbal supplements, OATP inhibitors, HIV medicines, statins	Concomitant medication† • Allowed medication included; anticoagulants, antihypertensives, erythropoietin, diuretics, statins, hypoglycemic agents, antidepressants. • Disallowed medication; known hepatotoxic drugs, strong/moderate CYP450 inhibitors, named HIV medicine, proton pump inhibitors, herbal supplements	Concomitant medication† • Disallowed medications included; strong CYP3A/P-gp inhibitors, OATP inhibitors, all HMG-CoA reductase inhibitors, and medicines of the proton pump inhibitor class	Concomitant medication† • Allowed medication included; named anticoagulants, named antihypertensives, erythropoietin, diuretics, statins, hypoglycaemic agents, antidepressants. Disallowed medication; known hepatotoxic drugs, herbal supplements, strong and moderate CYP3A/p-gp inhibitors, named HIV medicine
Primary outcome (including scoring methods and timing of assessments)	Primary outcome • SVR12; blood test 12 weeks following the end of all treatment, using LLoQ <15 IU/mL • Safety and tolerability during therapy and follow-up	Primary outcome • SVR12; blood test 12 weeks following the end of all treatment, using LLoQ <15 IU/mL • Safety and tolerability during therapy and follow-up	Primary outcome • SVR12; blood test 12 weeks following end of treatment using LLoQ <25IU/mL TND or TDu • Safety and tolerability during therapy and follow-up	Primary outcome • SVR12; blood test 12 weeks following end of treatment using LLoQ <15IU/mL • Safety and tolerability during therapy and follow-up
Secondary/other objectives *Not reported in this submission*	Secondary objectives • SVR 24 weeks Other objectives • Evaluate the efficacy of EBR/GZR by the proportion of patients in the immediate treatment arm achieving SVR24 • Evaluate the efficacy of EBR/GZR as assessed by the proportion of patients in the immediate treatment arm achieving undetectable HCV RNA and HCV RNA < LLoQ at	Secondary objectives • SVR 24 weeks Other objectives • Evaluate EBR/GZR+/- RBV assessed by the proportion of patients achieving undetectable HCV RNA and HCV RNA <LLoQ at weeks 2, 4, 12, and follow up week 4 (SVR4) • Describe and compare patient reported outcomes related to HRQoL, fatigue, and work productivity/activity impairment	Secondary objectives • Evaluate EBR/GZR assessed with or without RBV as assessed by the time to achieve TND HCV RNA levels • Evaluate the efficacy in each treatment arm as assessed by the proportion of patients achieving TND HCV RNA levels and HCV RNA levels <25 IU/mL [TD(u)] at Week 2, Week 4, and end of treatment visit (Week 12). • Evaluate the efficacy in each treatment arm as assessed by	Secondary objectives • Evaluate EBR/GZR assessed by proportion of patients in the immediate treatment arm achieving SVR24 • Evaluate EBR/GZR assessed by proportion of patients in the immediate treatment arm achieving undetectable HCV RNA <LLoQ at Weeks 2, 4 and 12 and Follow-Up Week 4 (SVR4). • Describe and compare patient reported outcomes related to HRQoL before, during, and

Criteria	C-EDGE TN[59] NCT02105467	C-EDGE TE[60] NCT02105701	C-SCAPE[62] NCT01932762	C-EDGE CO-STAR[63] NCT02105688
	Weeks 2, 4, 12 and Follow-Up week 4 (SVR4). • Describe and compare patient-reported outcomes related to HRQoL, fatigue, and work productivity/activity impairment before, during, and after treatment with EBR/GZR versus placebo. • Evaluate the emergence of RAVs to GZR or EBR when administered as part of a combination regimen. • Evaluate PK of EBR/GZR • Explore relationship between genetic variation and patient response to treatment administered	before, during, and after treatment with EBR/GZR+/- RBV • Evaluate the emergence of RAVs to GZR or EBR +/- RBV • Evaluate PK of EBR/GZR+/- RBV • Explore relationship between genetic variation and patient response to treatment administered • In HIV co-infected patients only, evaluate proportion of patients who develop HIV-1 virological failure during protocol therapy. • Evaluate effect of study regimen on CD4+ cell counts in HIV co-infected patients only	the proportion of patients achieving SVR4, SV24 • evaluate the emergence of antiviral resistance EBR/GZR with RBV	after treatment with EBR/GZR vs. placebo • Evaluate the emergence of RAVs to GZR or EBR • Evaluate PK of EBR/GZR • In HIV co-infected patients only, evaluate proportion of patients who develop HIV-1 virological failure during protocol therapy • Evaluate effect of study regimen on CD4+ cell counts in HIV co-infected patients only.
Post Hoc analysis	• SVR12 (GT1a, GT1b, GT4) split by cirrhosis stage in TN patients • Safety (GT1 or GT4) split by cirrhosis stage	• SVR12(GT1a, GT1b, GT4) split by cirrhosis stage in TE patients • Safety (GT1 or GT4) split by cirrhosis stage	• SVR12 (GT4) in TN patients split by cirrhosis stage • Safety split by cirrhosis stage	• SVR12 (GT1a or GT1b) split by cirrhosis stage in treatment naïve patients • Safety GT1 split by cirrhosis stage

Abbreviations. CSR, clinical study report; EBR/GZR, Elbasvir/Grazoprevir; HRQOL, health related quality of life; OATP, Organic Anion Transporting Polypeptide; LLoQ, Lower limit of quantification; mFAS, modified full analysis set; TBC, to be confirmed

† This is not an exhaustive list. Please see Appendix 5 for full details for each study

Table 24 Comparative summary of trial methodology (2)

Criteria	C-SURFER[14] NCT02092350	C-WORTHY[61] NCT0171326	C-EDGE H2H[64] NCT02358044
Study location	• 68 Study centres • 12 countries; USA, Argentina, Australia, Canada, Estonia, France, Israel, South Korea, Lithuania, Netherlands, Spain, and Sweden	• 75 study centres • 12 countries; United States, Australia, Canada, Denmark, France, Hungary, Israel, New Zealand, Puerto Rico, Span, Sweden, and Turkey	• 32 study centres • 9 countries: Czech Republic, Denmark, Hungary, Lithuania, Norway, Poland, Romania, Spain, and Turkey
Trial design	• Phase III • Randomised, double blind controlled (patients blind, study administrator blind) • Cross over treatment arm, which was open-label treatment arm (deferred group to EBR/GZR)	• Phase II • 4 part study including; randomised and open-label treatment arms • Parallel group *Treatment arms of interest to this submission are: A3, B3, B5, B9, and B13*	• Phase III • Open label, randomised active control trial
Eligibility criteria	• Chronic HCV GT1 • Treatment naïve or prior treatment failure with IFN or PEG-IFN or PR intolerant • Cirrhotic or non-cirrhotic • Aged ≥18 years • CKD stages 4-5 (with or without haemodialysis) • HCV≥10,000IU/mL at screening	<u>Treatment arm A3</u> • Chronic HCV GT1b • Treatment naïve • Non-cirrhotic • Aged ≥18 years • HCV≥10,000IU/mL at screening <u>Treatment arm B3, B5, B9, B13</u> • Chronic HCV GT1a and 1b • Treatment naïve and treatment experienced patients • Cirrhotic or non-cirrhotic • Aged ≥18 years • HCV≥10,000IU/mL at screening • B13, included HIV co-infected patients <u>Treatment arm C and D</u> • Not relevant to this submission.	• Chronic HCV GT1, GT4, or GT6 • Treatment naïve or experienced • Cirrhotic or non-cirrhotic • Aged ≥18 years • HCV≥10,000IU/mL at screening
Trial drugs (intervention, details for administration,	<u>Intervention</u> • EBR(50mg)/GZR(100mg) FDC tablet • 12 weeks, taken once daily without	<u>Intervention</u> • EBR(50mg)/GZR(100mg) FDC tablet • 12 weeks, taken once daily without	<u>Intervention</u> • EBR(50mg)/GZR(100mg) 12 weeks

Criteria	C-SURFER[14] NCT02092350	C-WORTHY[61] NCT0171326	C-EDGE H2H[64] NCT02358044
posology)	regard to food Comparator Placebo	regard to food Comparator • No active control	Comparator • SOF (400mg) once daily+Peg-IFN 1.5mcg per Kg once weekly, and RBV 1000-1200mg twice daily for 12 weeks
Concomitant medication	Concomitant medication† • Allowed medication; anticoagulants, hypoglycemic agents, diuretics, hyperthyroidism. • Disallowed medication; known hepatotoxic drugs, herbal supplements, CYP3A/P-gp inhibitors, OATP inhibitors, HIV medicines, statins	Concomitant medication† • Allowed medication; anticoagulants with narrow therapeutic ranges (i.e. warfarin), amiodarone, sildenafil etc. note patients were closely monitored), Silymarin (Milk Thistle, Silybun marianum). • Disallowed medication; strong CYP3A/P-gp inhibitors, OATP inhibitors, named HIV medications (allowed: Dolutegravir, Raltegravir, rilpilvirine, Tenofovir, Lamivudine, Abacavir and Emtricitabine, arm B13 only), proton pump inhibitors, H2 antagonists, anti-ulcer/gastric acid suppressants, investigational agents, corticosteroids, herbal supplements (except Silymarin).	Concomitant medication† • Disallowed medication included; hepatotoxic drugs, named herbal supplements, strong CYP3A/P-gp inducers, OATP inhibitors, and, named HIV medications.
Primary outcome (including scoring methods and timing of assessments)	Primary outcome • SVR12; blood test 12 weeks following the end of all treatment, using LLoQ <15 IU/mL • Safety and tolerability during therapy and follow-up	Primary outcome • SVR12; blood test 12 weeks following the end of all treatment, using LLoQ <15 IU/mL • Safety and tolerability during therapy and follow-up	Primary outcomes • SVR12; blood test 12 weeks following end of treatment using LLoQ <15IU/mL • Safety and tolerability during therapy and follow-up
Secondary/other objectives	Secondary objectives • Analysis of RAVs among virological failures Other objectives • Evaluate the efficacy of EBR/GZR assessed by the proportion of patients achieving:	Secondary objectives • Evaluate efficacy by the time to first achievement of undetectable HCV RNA • Evaluate the efficacy of each treatment arm as assessed by the proportion of patients achieving undetectable HCV RNA and HCV RNA <25 IU/mL at week 2, 4, and end of treatment visit for the 8	Secondary objectives • Evaluate safety profile of EBR/GZR as compared to SOF+PR as assessed by the proportion of patients experiencing a tier 1 safety event, defined as: ○ Any drug related SAE ○ any drug-related AE leading to permanent discontinuation of all

Criteria	C-SURFER[14] NCT02092350	C-WORTHY[61] NCT0171326	C-EDGE H2H[64] NCT02358044
	• SVR24 HCV RNA <LLoQ (either TD(u) or TND) • SVR4 HCV RNA <LLoQ (either TD(u) or TND) • SVR 12 HCV RNA <LLoQ (either TD(u) or TND) for the deferred treatment arm • SVR12 HCV RNA <LLoQ (either TD(u) or TND) for all active and treatment arms combined • Evaluate the safety and tolerability of EBR/GZR for all treatment arms • Evaluate the emergence of RAVs to GZR or EBR • Evaluate PK of EBR/GZR • Evaluate PK/PD relationship EBR/GZR plasma levels in relation to efficacy and safety • Evaluate biomarkers that may be predictive of tolerability of study drugs and virologic response to EBR/GZR by comparing biomarker levels over time in patients who respond or fail study therapy. • describe and compare changes from baseline HRQoL during and after active and placebo treatment periods • Assess the genetic variation in the human IL28B gene as a predictor of virologic response in each treatment arm • Determine the impact of HCV treatment on cryoglobulinemia in patients with CKD	and 12-week duration arms and, week 2, 4, 12, and end of treatment visit for the 18-week duration arm. • Evaluate efficacy in patients achieving SVR4, and SVR24 • Evaluate the emergence of RAVs to EBR or GZR+/- RBV • Evaluate HIV-1 virologic failure during protocol therapy (only applicable to part B for co-infected HIV patients) • Evaluate the effect of the study regimen on CD4+ T-cell counts (only applicable to part B for co-infected HIV patients) <u>Other objectives</u> • Evaluate PK of EBR/GZR+/- RBV • Assess the genetic variation in the human IL28B gene as a predictor of virologic response in each treatment arm • Evaluate biomarkers that may be predictive of tolerability of study drugs and virologic response o EBR/GZR+/- RBV by comparing biomarker levels over time in patients who respond. • Describe changes from baseline in HRQoL during and after treatment with EBR/GZR • Assess the association between baseline CD4+ Tcell count and achieving HCV SVR12 for HIV co-infected patients	study drugs ○ neutrophil count <0.75 × 109/L ○ hemoglobin <10 g/dL ○ any event leading to discontinuation of study drug • To evaluate whether EBR/GZR has superior efficacy to SOF+PR in the treatment of HCV, as assessed by the proportion of patients achieving SVR12, defined as HCV RNA < LLOQ (either TD[u] or TND) 12 weeks after the end of all study therapy <u>Other objectives</u> • Describe and compare patient reported outcomes related to HRQoL, fatigue, and work productivity/activity impairment before, during, and after treatment with EBR/GZR+/- RBV vs. SOF+PR • Evaluate the efficacy of EBR/GZR and SOF+PR, as assessed by the proportion of patients achieving SVR24, defined as HCV RNA < LLOQ (either TD(u) or TND) 24 weeks after the end of all study therapy • Evaluate the efficacy of EBR/GZR and SOF+PR, as assessed by the proportion of patients achieving HCV RNA < LLOQ (either TND(u) or TND) at Week 2, 4, 12, and Follow-up Week 4 (SVR4). • Evaluate the efficacy of EBR/GZR and SOF+PR in subgroup populations. These subgroups include but are not limited to patients with cirrhosis, presence of IL-28 polymorphism, GT1b vs. non-1b, and

Criteria	C-SURFER[14] NCT02092350	C-WORTHY[61] NCT0171326	C-EDGE H2H[64] NCT02358044
			higher baseline HCV RNA. • Evaluate the emergence of viral resistance-associated variants (RAVs) to EBR and/or GZR when administered as part of a combination regimen • Explore the relationship between genetic variation and response to the treatment(s) administered.
Post Hoc analysis	• SVR12 (GT1a or GT1b) split by cirrhosis stage and treatment experience • Safety GT1 split by cirrhosis stage	• SVR (GT1a and GT1b) split by cirrhosis stage and treatment experience • Safety GT1 split by cirrhosis stage	• SVR (GT1a, GT1b and GT4) split by cirrhosis stage and treatment experience • Safety GT1 and GT4 split by cirrhosis stage

Abbreviations. CSR, clinical study report; EBR/GZR, elbasvir/grazoprevir; HRQOL, health related quality of life; OATP, Organic Anion Transporting Polypeptide; LLOQ, Lower limit of quantification; mFAS, modified full analysis set; TBC, to be confirmed

† This is not an exhaustive list. Please see Appendix 5 for full details for each study.

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

4.4.1 Statistical analysis

The statistical analysis plan for each included clinical trial has been summarised below according to the available CSR. The statistical analysis and definition of study groups described below does not explicitly relate to the study groups considered in the post-hoc analysis, which have been used for the NMA reported in section 4.10. However, to demonstrate the robust design of the EBR/GZR trials this section has been completed according to the primary efficacy endpoint and the safety analyses; as it is these outcomes that will be used in the NMA.

C-EDGE TN Study, NCT02105467[56, 59]

Primary hypothesis

The primary hypothesis was that the number of patients receiving EBR/GZR in the immediate treatment arm would be superior to a SVR12 of 73%. This historical SVR12 value of 73% was derived from phase III trials of SMV and PR in the treatment of TN HCV mono-infected patients after adjustment for the expected proportion of cirrhotic patients, and the anticipated improved tolerability expected with an interferon-free regimen[68, 69].

Interim analysis and stopping guidelines

There were no formal interim analyses planned or performed for C-EDGE TN. Non-blinded medical monitoring teams were responsible for the review of SAE's as needed, to ensure the safety of the patients participating in the study.

Statistical methods used to compare groups for primary outcome

Sample Size

The study protocol originally planned to enrol approximately 400 patients, with 300 patients in the immediate treatment arm and 100 in the placebo (deferred) treatment arm.

SVR12 was reported using the full analysis set (FAS), which consisted of all patients randomised to the immediate treatment group and who received at least one dose of study medication. The deferred treatment group served as a control for the first 12 weeks of active therapy. Assuming a response rate of 85%, the immediate treatment group had over a 99% power to demonstrate a SVR12 superior to the 73% historical control at an overall one-sided 2.5% α-level. However, due to the small number of patients that did not achieve an SVR12, the two-sided one-sample exact test was used to test the null hypothesis, and the Clopper-

Pearson method was used to construct the 95% confidence intervals. To assess safety (primary objective) the all patients as treat population (APaT), defined as all patients who received at least one dose of study medication, was used to compare patients randomised to the immediate treatment group compared with placebo during the initial blinded treatment period plus the first 14 days of follow-up. Statistical analysis was performed using the Miettinen and Nurminen method using the immediate and deferred treatment groups during the blinded phase plus the first 14 days of follow-up; this method was used for the construct of between-treatment 95% confidence intervals and p-values.

C-EDGE TE Study NCT02105701[60]

Primary hypothesis

The primary hypothesis states that at least one of the treatment arms in C-EDGE TE will achieve SVR12 that is superior to a historical SVR rate of 58%. This value was based on the lack of an approved all-oral regimen for this population at the time of protocol design. The historical reference rate of 58% was derived from a phase 2b registration trial of SMV 100mg or 150mg daily for 12, 24, or 48 weeks in combination with PR for 48 weeks in TE patients. Adjustments were made to account for the proportion and underlying difference observed in treatment experienced patients described as null (SVR 45%) and partial responders (SVR 70%); additional consideration was also given for the improved safety associated with an IFN-free regimen (full details available in section 9.2.1 of the CSR).

Interim analysis and stopping guidelines

There were no formal interim analyses planned or performed for C-EDGE TE.

Statistical methods used to compare groups for primary outcome

Sample Size

The study protocol originally planned to enroll 400 patients (stratified according to treatment experience (response type) and presence of cirrhosis (yes or no)); this would provide 99% power to demonstrate the primary hypothesis. The power calculation is based on the assumption of an underlying response rate of at least 80% in the treatment arms.

The study protocol planned to use Wald-Test, using a two-sided 95% asymptomatic confidence interval. However, due to the small number of patients who did not achieve SVR12 the results of this method were considered unreliable. Therefore, the Clopper-Pearson method was used to construct the 95% confidence interval for SVR12. The minimum number of patients needed to achieve the primary endpoint (SVR12) was 69/100 (69%) (per treatment arm) with 95% CI of 58.6% to 79.4%. Safety and tolerability was assessed by a clinical review of all AEs and laboratory parameters. Each statistical test was

conducted at α=0.025 two-sided level to control for overall type-1 error at the two-side α=0.05 level. The probability of observing at least one specific AE was dependant on the number of patients treated, and the underlying percentage of patients with that AE in the study population. This was based on the exact binomial method Clopper and Pearson. For example, if the underlying incidence of a specific AE was 1.5%, there was a 78% chance of observing at least one incident of that specific AE among 100 patients in this study.

C-SCAPE Study NCT01932762[62]

Primary hypothesis

No formal hypothesis was reported. The primary objectives were: the proportion of patient receiving EBR/GZR achieving SVR12, and to evaluate the safety and tolerability of EBR/GZR.

Interim analysis and stopping guidelines

The CSR did not report any formal interim analysis planned or performed for C-SCAPE.

Statistical methods used to compare groups for primary outcome

Sample Size

A total of 68 patients were enrolled, of which 38 were randomised (1:1 ratio) into either treatment arm B2 (n=19) or B3 (n=19, arm of interest). SVR12 was calculated using the proportion of patients achieving this measure within the per-protocol population (PP). Assuming a protocol violation rate of 10% the PP population was to include 18 patients. If the true SVR12 rate is approximately 80% or 90% the 95% CI were 52.4%- 96.3% or 65.3%-98.6%, respectively. The 95% CI were calculated using the Clopper-Pearson method. The primary safety objective of this study was assessed by a review of the accumulated safety data. The Clopper-Pearson method was used to construct 95% CI. The CSR reports the likelihood of the true proportion of patients with a particular AE based on the observed number of events reported, i.e. if a particular AE was not reported in a sample of 20 patients, then with 95% confidence we can say that the true proportion is no more than 16.8%.

C-EDGE CO-STAR Study NCT02105688[63]

Primary hypothesis

The study hypothesis was that the proportion of patient receiving EBR/GZR in the immediate treatment arm achieving SVR12 will be superior to 67%. This value was derived from the phase II trials of SOF in HCV GT1 patients co-infected with HIV (PHOTON-1), which reported an overall SVR12 of 76%. To adjust for the expected higher proportion of patients described as cirrhotic (reduction of SVR by 1%), the improved safety profile of an IFN-free regimen (reduction of SVR by 5%), and the uncertainty associated with a "high risk behaviour" population (reduction of SVR by 3%) the historic SVR12 was calculated at 67%.

Interim analysis and stopping guidelines

There were no formal interim analyses planned or performed for C-COSTAR. Periodic safety analyses were conducted and reviewed by the unblinded medical team at regular intervals to ensure the safety of the patients participating in the clinical trial.

Statistical methods used to compare groups for primary outcome

Sample Size

A total of 301 patients were randomised (2:1 ratio) into either the immediate (n=201) or deferred (n=100) treatment groups. For the safety analysis the deferred treatment arm served as a placebo control in the power estimation.

Assuming a response rate of at least 85% in the immediate treatment arm, the study had over 99% power to demonstrate that SVR12 was superior to the historical SVR12 rate of 67% at an overall one-sided 2.5% alpha-level. The power and sample size calculations were based on the additional assumption that approximately 20% of patients would not be included in the analyses related to early discontinuation with reasons unrelated to HCV treatment. Due to the small number of patients who did not achieve SVR12, the Clopper-Pearson method was used to construct the 95% confidence intervals for the SVR12 rate, versus the planned Wald test. The primary safety objective compared patients randomised to the immediate treatment arm with patients randomised to the deferred treatment arm during the initial blinded treatment period. The power to detect a difference in AEs between these two groups use a one-sided 2.5% alpha level if the immediate treatment arm had a two-fold or three fold-increment in AE rate, i.e. if the true event rate reached 20% or 40% with a two-fold increment in the deferred or immediate treatment arm, respectively; then the power to detect a difference was 95% at a two-sided 2.5% alpha level.

C-SURFER Study NCT02092350[14]

Primary hypothesis

The primary hypotheses was that the proportion of HCV GT1 infected CKD 4-5 patients achieving SVR (defined as HCV RNA <LLoQ 12 weeks after the end of all study therapy) will be superior to 45%. This historical value was based on the findings of two studies; the first, a meta-analysis that reported a SVR12 rate of 39% in patients with CKD stages 3-5 and HCV co-infection who had been treated with IFN monotherapy[70]; the second, a study reporting a SVR12 rate of 40% in patients with HCV GT1 infection without renal disease receiving PR[71].

Interim analysis and stopping guidelines

There were no formal interim analyses planned or performed for C-SURFER. Periodic safety analyses were conducted and reviewed by an external data monitoring committee to ensure the safety of the patients participating in the study.

Statistical methods used to compare groups for primary outcome

Sample Size

The study protocol originally planned to enroll approximately 105 patients into both the immediate and deferred treatment groups. In addition, it was planned that 10 patients would be enrolled into the intensive PK treatment group (Figure 6).

This study would have at least 95% power to demonstrate a SVR12 rate for EBR/GZR that was higher than the reference SVR12 rate of 45% at an overall one-sided 2.5% α-level, if the true SVR12 rate of EBR/GZR was ~65%. The power and sample size were based on the assumption that approximately 10% of the randomised patients would have a missing SVR12 rate related to death or early discontinuation from study due to reasons unrelated to their response to HCV treatment; these patients would be excluded from the mFAS population. Due to the small number of patients who did not achieve SVR12, the Clopper-Pearson method was used to construct the 95% confidence intervals for the SVR12 rate versus the planned Wald test. To assess safety and tolerability, power calculations were based on various assumptions about the true AE rate in the deferred treatment arm, and assumed 105 patients in each arm; with a power to detect a difference at a 2-sided 2.5% α-level at 97% if the true event rate in the deferred and immediate treatment arm was 25% and 50%, respectively. Statistical analyses were performed using the Miettinen and Nurminen method stratified by dialysis status at baseline.

C-WORTHY Study NCT01717326[61]

Primary hypothesis

This was a hypothesis generating study therefore there was no formal hypothesis for this study, and no active or historical control. The primary objectives included efficacy SVR12 and the safety and tolerability of EBR/GZR.

Interim analysis and stopping guidelines

There were no formal interim analyses planned or performed.

Statistical methods used to compare groups for primary outcome

Sample Size

A total of 136 patients were randomised to one of the five relevant treatment arms. For treatment Part A, assuming a protocol violation rate of 10%, the PP population was expected to include 11 patients within each arm. If the SVR12 rate is 90.9% this would represent 10/11 patients with a two-sided 95% confidence interval of 58.7%-99.8%. For treatment Part B, assuming a protocol violation rate of 10%, the PP was expected to include 27 patients; if the SVR12 rate is 92.6%, this would represent 25/27 patients with a two-sided 95% confidence interval of 75.7%-99.1%. To estimate the true proportion of patients with an AE, the upper 95% confidence interval was calculated using the two-sided 95% Clopper-Pearson method. For example, if an AE was not observed in a population sample size of either 30 patients (part B) or 12 patients (part A) then it is possible to conclude that the upper bound of the two-sided 95% confidence for the true proportion of patients is no more than 11.6% and 26.5% in the two sample sizes, respectively.

C-EDGE H2H Study NCT02358044[64]

Primary hypothesis

The primary hypothesis stated that the proportion of patients achieving SVR12 in the EBR/GZR arm is non-inferior to the SOF+PR arm.

Interim analysis and stopping guidelines

The CSR did not report any formal interim analysis planned or performed for C-EDGE H2H.

Statistical methods used to compare groups for primary outcome

Sample Size

The study planned to enrol 244 patients in a 1:1 ratio, and would provide 90% power to demonstrate that EBR/GZR is non-inferior to SOF+PR using a non-inferiority margin of 10% and a one-sided 0.25 alpha level if the true SVR12 rates were 90% for EBR/GZR and 86% for SOF+PR. Non-inferiority was determined based on the entire effect of the active control assumed to be present in the current study, and the specification of the largest clinically acceptable difference between the test drug and the active control. The Meittinen and Nurminen method with stratification by GT1a vs GT non-1a, and fibrosis stage was used for the primary statistical analysis and the construct of CI.

4.4.2 Trial population included in primary analysis of the primary outcome and methods to take account of missing data

C-EDGE TN Study, NCT02105467[56, 59]

Efficacy analysis

The FAS population of the immediate treatment group (n=316) served as the primary population for SVR12, compared with the deferred (placebo) treatment group (n=105). The FAS population consisted of all randomised patients who had received at least one dose of study treatment.

Safety analysis

The APaT population was utilised for the safety analysis. This included all randomised patients who had received at least one dose of study treatment. Patients were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data. There were no patients who took incorrect study treatment for the entire treatment period. Thus the FAS and APaT populations are identical.

Missing data approach and censoring methods

For the primary efficacy (SVR12) endpoint the “missing = failure” (M=F) method was used. “Missing = failure” was defined as; the imputation of any non-intermittent missing data as failure, regardless of the reason for study discontinuation. Non intermittent missing data was described as: 1) missing values considered study drug related, i.e. missing values related to discontinuation due to treatment related reasons either for safety or efficacy; 2) missing values not considered to be study drug related, i.e. missing values related to discontinuation related to reasons such as; lost to follow-up, protocol violation, withdrawal of consent, administrative reasons. If a patient did not have a HCV RNA value at baseline/day 1, then this result was replaced with a screening result.

For the primary safety endpoint missing values were handled using the “Data as Observed” (DAO) approach. The DAO approach was defined as; any patient during the treatment period with a missing HCV RNA evaluation at any particular visit will be excluded from the analysis at that time point. However, a missing value for baseline/day 1 results was replaced with a screening result if available.

C-EDGE TE Study NCT02105701[60]

Efficacy analysis

The FAS population (n=420) was used for the primary efficacy endpoint SVR12. Relevant to this submission is treatment arm A (n=105), this included patients with GT1a, GT1b, and GT4 infections treated with EBR/GZR 12 weeks. The FAS population consisted of all randomised patients who had received at least one dose of study medication.

Safety analysis

The APaT population was utilised for the safety analyses. This included all randomised patients who had received at least one dose of study treatment. Patients were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data. All patients who received at least one dose of study medication also had safety follow-up, and no patient received the wrong study medication. Therefore, the FAS and APaT are the same for this study.

Missing data approach and censoring methods

For SVR12 the M=F method was used. “Missing = failure” was defined as; the imputation of any non-intermittent missing data as failure, regardless of the reason for study discontinuation. Non intermittent missing data was described as: 1) missing values considered study drug related, i.e. missing values due to discontinuation due to treatment related reasons either for safety or efficacy: 2) missing values not considered to be study drug related, i.e. missing values due to discontinuation due to reasons such as; loss to follow-up, protocol violation, withdrawal of consent, administrative reason. If a patient did not have a HCV RNA value at baseline/day 1, then this result was replaced with a screening result.

For the safety endpoint missing values were handled using the DAO approach. The DAO approach was defined as; any patient during the treatment period with a missing HCV RNA evaluation at any particular visit will be excluded from the analysis at that time point.

C-SCAPE Study NCT01932762[62]

Efficacy analysis

The PP population (n=19) served as the primary population for the SVR12 efficacy outcome in patients randomised to treatment arm B3. The PP population excludes patients with important deviations from the protocol that may substantially affect the results of the primary or secondary efficacy endpoints. Protocol violations included; non-relevant/mixed (non GT4) infections, patients in receipt of prohibited concomitant medications as described in section 4.3.

Safety analysis

The APaT population was utilised for the safety analysis. This includes all patients who received at least one dose of study treatment. Patients were included in the treatment arm corresponding to the treatment they actually received.

Missing data approach and censoring methods

For the primary efficacy (SVR12) endpoint the method "observed failure was used". Observed Failure (OF) approach was described as patients who: 1) discontinued assigned treatment early due to lack of efficacy or 2) discontinued from the study following a confirmed HCV RNA TD (q) during follow-up are considered as failures thereafter. Otherwise, any patient missing an HCV RNA evaluation at any particular visit was excluded from the analysis at that time point. If a patient did not have a HCV RNA value at the last scheduled follow-up visit, but had a 12 week follow-up visit, then SVR12 would be used in place of SVR24. Similarly, a later follow-up value could be used to impute an earlier missed SVR assessment.

For the primary safety endpoint missing values were handled using the DAO approach. The DAO approach was defined as; any patient during the treatment period with a missing HCV RNA evaluation at any particular visit will be excluded from the analysis at that time point.

C-EDGE CO-STAR Study NCT02105688[63]

Efficacy analysis

The mFAS population (n=198), a subset of the FAS (n=201), served as the primary population for the SVR12 efficacy outcome in patients randomised to the immediate treatment arm. The mFAS excluded patients who were lost to follow-up, or discontinued the study for reasons unrelated to treatment regimen or their response to HCV treatment.

Safety analysis

The APaT population was utilised for the safety analysis. This included all randomised patients who had received at least one dose of study treatment. Patients were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data. In this study all patients randomised received the correct study medication.

Missing data approach and censoring methods

For the primary efficacy (SVR12) endpoint the "treatment related discontinuation = failure" (TRD=F) approach was used. This was described as non-intermittent missing study drug

related, and non-intermittent missing unrelated to study drug. For patients with a documented HCV failure during treatment or follow-up, even if they withdrew from the study early due to reasons not relating to study drug they were classified as treatment failures.

For the primary safety endpoint missing values were handled using the DAO approach. The DAO approach was defined as; any patient during the treatment period with a missing HCV RNA evaluation at any particular visit will be excluded from the analysis at that time point. However, a missing value for baseline/day 1 results was replaced with a screening result if available.

C-SURFER Study NCT02092350[14]

Efficacy analysis

The mFAS population, which consisted of the immediate treatment group (n=105) and the intensive PK group (n=10) served as the primary population for the for SVR12 efficacy outcome with patients excluded for the following reasons:

- Failure to receive at least one dose of study treatment
- Missing data due to death with reasons unrelated to study drug or reasons other than liver disease
- Missing data due to study discontinuation with reasons unrelated to progression of liver disease, study drug and their responses to the HCV treatment

Safety analysis

The APaT population was utilised for the safety analysis. This included all randomised patients who had received at least one dose of study treatment. Patients were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data.

Missing data approach and censoring methods

For the primary efficacy (SVR12) endpoint the TRD=F approach was used. This was described as non-intermittent missing study drug related, and non-intermittent missing unrelated to study drug. For patients with a documented HCV failure during treatment or follow-up, even if they withdrew from the study early due to reasons not relating to study drug they were classified as treatment failures. In addition, a missing baseline/Day1 HCV RNA result was replaced with a screening result, if available.

For the primary safety endpoint missing values were handled using the DAO approach. The DAO approach was defined as: any patient during the treatment period with a missing HCV RNA evaluation at any particular visit will be excluded from the analysis at that time point.

C-WORTHY Study NCT01717326[61]

Efficacy analysis

SVR12 was assessed using the PP population as the primary population; this represents 12 patients in treatment arm A3, 31 patients in treatment arm B3, 29 patients in treatment arm B5, 33 patients in treatment arm B9, and 28 patients in treatment arm B13. The PP population excluded patients due to important protocol deviations that could substantially affect the results of the primary and key secondary endpoints. These included: patients with non-GT1a or GT1b infection, mixed GT infection, non-typeable infection (part A), non-GT1 infection, mixed GT infection, or non-typeable infection (part B), patients who met the criteria for virologic failure but had undetectable EBR/GZR levels at the PK sampling time point associated with failure, and/or the patient received concomitant medication(s) that were described as prohibited.

Safety analysis

To assess safety (primary objective) the APaT population, defined as all patients who received at least one dose of study medication, was used. Patients were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data. For most patients this was the treatment group to which they were randomised. One patient who received incorrect study treatment for the entire treatment period was included in the treatment group corresponding to the study treatment actually received.

Missing data approach and censoring methods

For the primary efficacy (SVR12) endpoint the method OF was used; this was described as patients who: 1) discontinued assigned treatment early due to lack of efficacy or 2) discontinued from the study following a confirmed HCV RNA TD (q) during follow-up are considered as failures thereafter. Otherwise, any patient missing an HCV RNA evaluation at any particular visit was excluded from the analysis at that time point.

For the safety analysis missing values were handed using the DAO; that is, any missing values were excluded from the analysis.

C-EDGE H2H Study NCT02358044[64]

Efficacy analysis

The FAS population (n=257), which included all patients who received at least one dose of study medication, served as the primary population for SVR12. Of note, two patients were

excluded from the SOF+PR treatment arm as prior to receiving study drug these patients withdrew consent. Therefore, 255 patients were considered in the FAS population.

Safety analysis

The APaT population was utilised for the safety analysis. This includes all patients who received at least one dose of study treatment. Patients were included in the treatment arm corresponding to the treatment they actually received; all patients in this study received their allocated treatment.

Missing data approach and censoring methods

For the primary efficacy (SVR12) endpoint the M=F method was used. “Missing = failure” was defined as; the imputation of any non-intermittent missing data as failure, regardless of the reason for study discontinuation. Non intermittent missing data was described as: 1) missing values considered study drug related, i.e. missing values due to discontinuation due to treatment related reasons either for safety or efficacy; 2) missing values not considered to be study drug related, i.e. missing values due to discontinuation due to reasons such as; loss to follow-up, protocol violation, withdrawal of consent, administrative reason. If a patient did not have a HCV RNA value at baseline/day 1, then this result was replaced with a screening result.

For the primary safety endpoint missing values were handled using the DAO approach. The DAO approach was defined as; any patient during the treatment period with a missing HCV RNA evaluation at any particular visit will be excluded from the analysis at that time point. However, a missing value for baseline/day 1 results was replaced with a screening result if available.

4.4.3 Statistical tests used in primary analysis

Table 25. Summary of statistical analyses in the RCTs

Trial, NCT number	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
C-EDGE TN [59] NCT02105467	• EBR/GZR is superior to a SVR12 of 73% in patients with GT1 (1a, 1b), 4, or 6, who are treatment naïve, and either cirrhotic or non-cirrhotic.	• The FAS population was used for the primary efficacy endpoint, SVR12 • The APaT population was used for the primary population for the safety analysis	• The study had >99% to demonstrate an SVR12 greater than 73% with a response rate of 85% based on the inclusion of 400 patients. • The power calculation for safety assumed 300 patients randomised to the immediate treatment arm and 100 patients randomised to the deferred treatment using Miettinen and Nurminen methods to determine between treatment differences.	Efficacy • M=F; any non-intermittent data study drug related or not was imputed as failure, regardless of the reason for study discontinuation Safety • In the absence of safety data the safety analysis used DAO, i.e. missing values were excluded.
C-EDGE TE [60] NCT02105701	• EBR/GZR is superior to a SVR12 of 58% in patients with GT1, 4, or 6, who are described as treatment experienced, and cirrhotic or non-cirrhotic.	• The FAS population was used for the primary efficacy endpoint, SVR12 • The APaT population was used for the primary population for the safety analysis	• The study had 99% power to demonstrate SVR12 greater than 58% with an assumed response rate of 69% based on the inclusion of 400 patients. • The power calculation for safety assumed 78% power to detect an underlying incidence of 1.5% for a specific AE in a sample size of 100 patients; 95% CI were calculated using the Clopper-Pearson method.	Efficacy • The handling of missing data was reported using the OF approach. This was described as Patients who; 1) discontinued assigned treatment early due to lack of efficacy or 2) discontinued from the study following a confirmed HCV RNA TD (q) during follow-up are considered as failures thereafter Safety • In the absence of safety data the safety analysis used DAO, i.e. missing values were excluded.
C-SCAPE [62] NCT01932762	• To assess the proportion of patients receiving EBR/GZR achieving SVR12	• The PP was used for the primary efficacy endpoint, SVR12 • The APaT population was used for the	• The study was powered to detect a true SVR rate of 80% assuming a discontinuation rate of 10% based on the inclusion of 19 patients. • The safety power calculation assumed	Efficacy • The handling of missing data was reported using the OF approach. This was described as Patients who; 1) discontinued assigned treatment

Trial, NCT number	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		primary population for the safety analysis	20 patients. If an AE was not detected, with 95% confidence it was possible to say that the true proportion of AEs was no more than 16.8%.	early due to lack of efficacy or 2) discontinued from the study following a confirmed HCV RNA TD (q) during follow-up are considered as failures thereafter. Safety • In the absence of safety data the safety analysis used DAO, i.e. missing values were excluded.
C-EDGE CO-STAR [63] NCT02105688	• EBR/GZR is superior to a SVR12 of 67% in patients with GT1, 4, and 6 TN, CNC, in receipt of opiate substitution therapy	• The mFAS was used for the primary efficacy endpoint, SVR12 • The APaT population was used for the primary population for the safety analysis	• The study had 95% power to detect an SVR12 rate greater than 67% based on a response rate of 85%, and an assumed a discontinuation rate of 20% based on the inclusion of 401 patients. • The power to detect a difference in AEs between the immediate and deferred treatment group was 95% of the true event rate reached 20% or 40%, respectively with a two sided 2.5% alpha level.	Efficacy • TRD=F (i.e. missing values dues to death, premature discontinuation, lack of efficacy) Safety • In the absence of safety data the safety analysis used DAO, i.e. missing values were excluded.
C-SURFER [14] NCT0209235	• EBR/GZR is superior to a SVR12 of 45% in patients with GT1 TN C/NC, with CKD 4-5	• The mFAS population was used for the primary efficacy endpoint, SVR12 • The APaT population is the primary population for the safety analysis	• The study had 95% power to demonstrate an SVR12 greater than 45% based on the planned inclusion of 105 patients per treatment arm. • The power calculation for safety assumed 105 patients randomised to each treatment arm using Miettinen and Nurminen methods to determine between treatment differences.	Efficacy • TRD=F (i.e. missing values dues to death, premature discontinuation, lack of efficacy) Safety • In the absence of safety data the safety analysis used DAO, i.e. missing values were excluded.
C-WORTHY [61] NCT01717326	• No formal hypothesis, this study was hypothesis generating	• The PP population was used for the primary efficacy analysis. • The APaT population	• The study was powered to demonstrate an SVR12 of approximately 90% assuming a 10% protocol violation rate in study parts A and B.	Efficacy • The handling of missing data was reported using the OF approach. This was described as Patients who; 1) discontinued assigned treatment

Trial, NCT number	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		was used for the primary population for the safety analysis.	• Using the upper 95% confidence interval, constructed using the Clopper-Pearson method, it was possible to detect the true proportion of patients in with an AE.	early due to lack of efficacy or 2) discontinued from the study following a confirmed HCV RNA TD (q) during follow-up are considered as failures thereafter. Safety • In the absence of safety data the safety analysis used DAO, i.e. missing values were excluded.
C-EDGE H2H [64] NCT02358044	• The proportion of patients achieving SVR12 in the EBR/GZR arm is non-inferior to the SOF+PR arm using a non-inferiority margin of 10%	• The FAS population was used for the primary efficacy endpoint. • The APaT population was used for the primary population for the safety analysis	• The study would provide 90% power to demonstrate that EBR/GZR is non-inferior (10% margin) to SOF+PR with a 1 sided 2.5% alpha level if the true SVR12 for EBR/GZR was 90% and 86% for SOF+PR • The Meittinen and Nurminen method with stratification by GT1a vs GT non-1a, and fibrosis stage was used for the primary statistical analysis and construct of 95% CI.	Efficacy • M=F; any non-intermittent data study drug related or not was imputed as failure, regardless of the reason for study discontinuation Safety • In the absence of safety data the safety analysis used DAO, i.e. missing values were excluded.

Abbreviations. CKD, chronic kidney disease; C/NC cirrhotic and non-cirrhotic; DAO, data as observed; EBR/GZR, grazoprevir/elbasvir; M=F, missing = failure; mFAS, modified full analysis set; OF, observed failure; SVR, sustained virological response; TD, target detected; TRD=F, treatment discontinuation = failure.

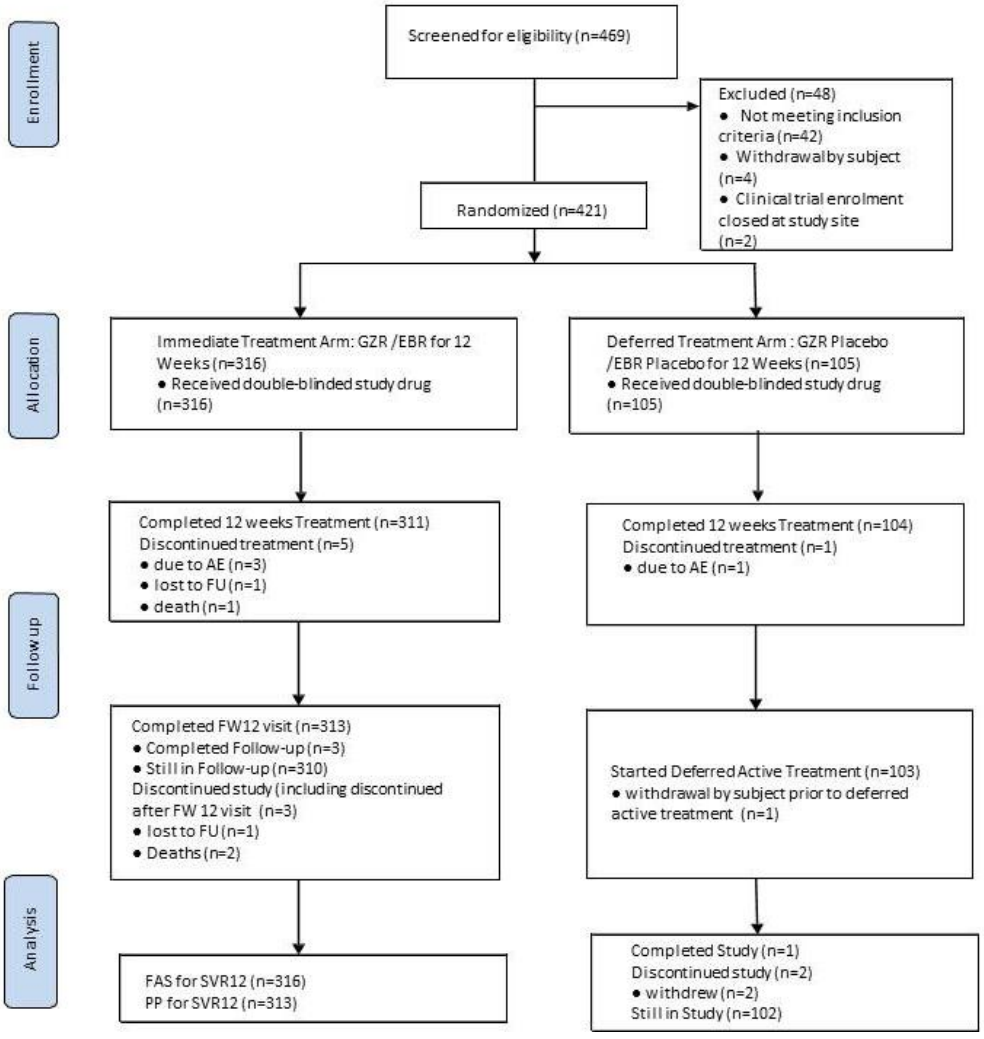
4.5 *Participant flow in the relevant randomised controlled trials*

4.5.1 Number of patients eligible to enter each trial, and crossover criteria

C-EDGE TN Study, NCT02105467[59]

Participant enrollment, randomisation, and disposition have been described in Appendix 5. Study disposition is illustrated in Figure 9. Demographic and baseline characteristics were generally balanced between the immediate- and deferred-treatment groups and are further described in Appendix 5, with a summary of patient characteristic reported in Table 26.

Figure 9. C-EDGE TN - Consort diagram

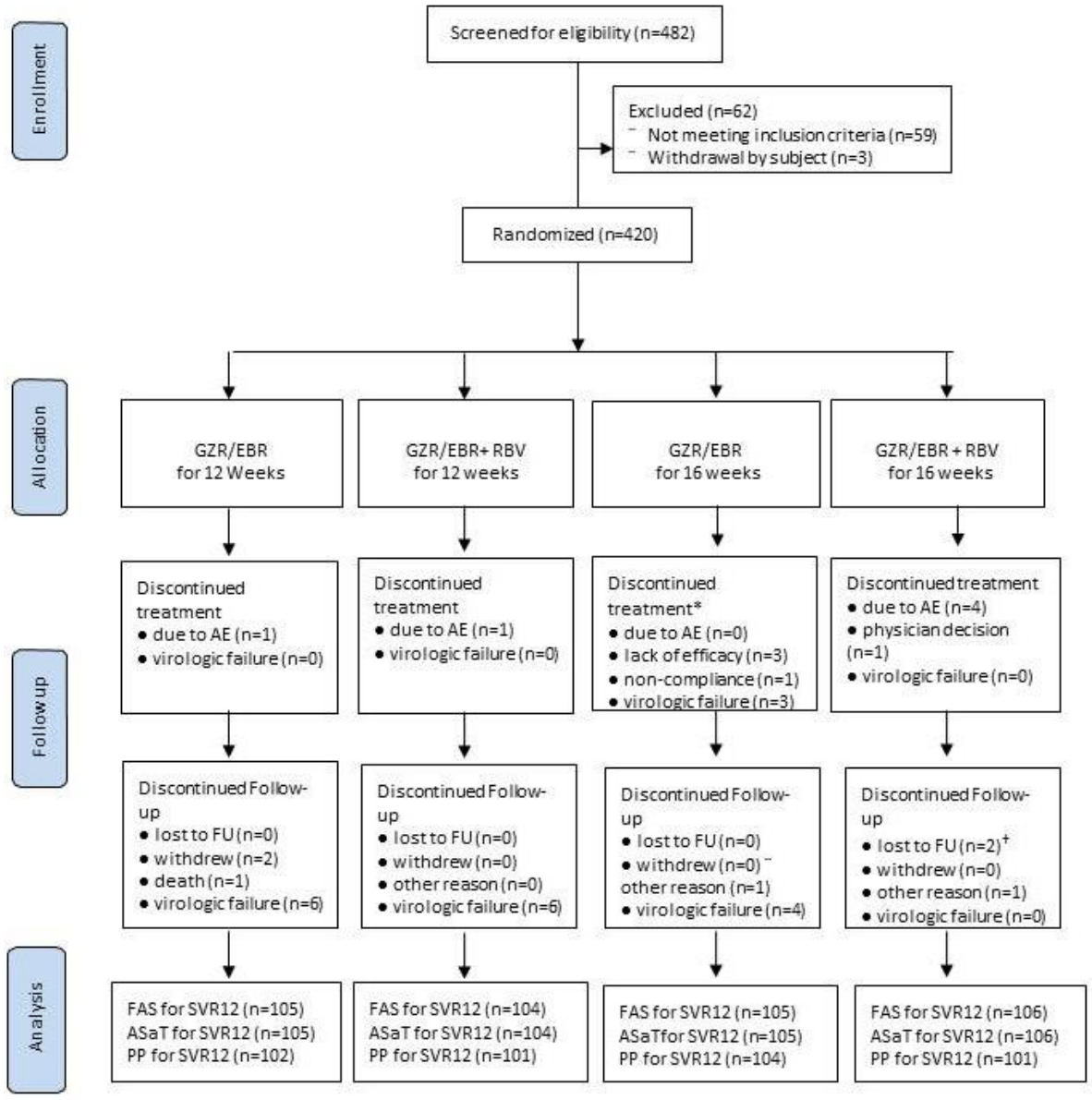


Abbreviations. AE, Adverse Event; FAS, full analysis set, FU, follow up; PP, Per Protocol

C-EDGE TE Study NCT02105701[60]

Participant enrollment, randomisation, and disposition have been described in Appendix 5. Study disposition is illustrated in Figure 10 below. Demographic and baseline characteristics were roughly equally distributed across the treatment arms and are further described in Appendix 5, with a summary of patient characteristic reported in Table 26.

Figure 10. C-EDGE TE - Consort diagram



Abbreviations. EBR/GZR, Grazoprevir/Elbasvir; RBV, Ribavirin; PP, Per Protocol; FAS, Full Analysis Set; FU, Follow up; ASaT, All-Patients-as-Treated population

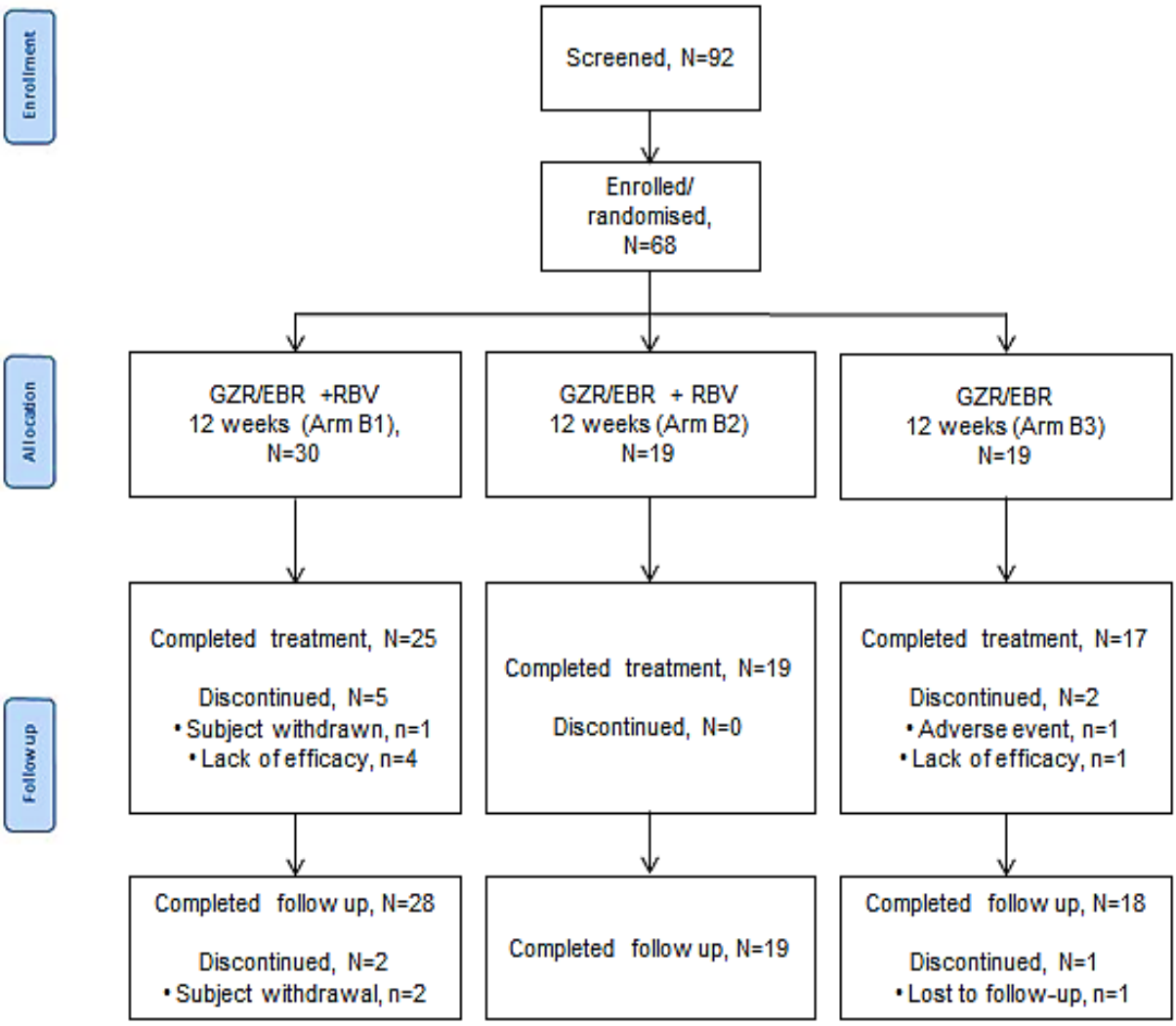
*One patient had missing data for status at the end of the treatment phase; this patient completed the study but was counted as having neither discontinued treatment nor completed treatment in the Patient Disposition (Table 10-1, CSR) and instead has a status of "Status Not Recorded."

†One patient has a status that is not recorded; this patient missed the FU12 visit due to relocation but may not be completely lost to follow-up.

C-SCAPE Study NCT01932762[62]

Participant enrollment, randomisation, and disposition have been described in Appendix 5. Study disposition is illustrated in Figure 11 below. The patient characteristics described for the treatment arms of interest were generally similar compared with the overall population and is further described in Appendix 5. However, the majority of patients in this treatment arm were infected with HCV GT4 as summarised in Table 26 .

Figure 11. C-SCAPE - Consort diagram

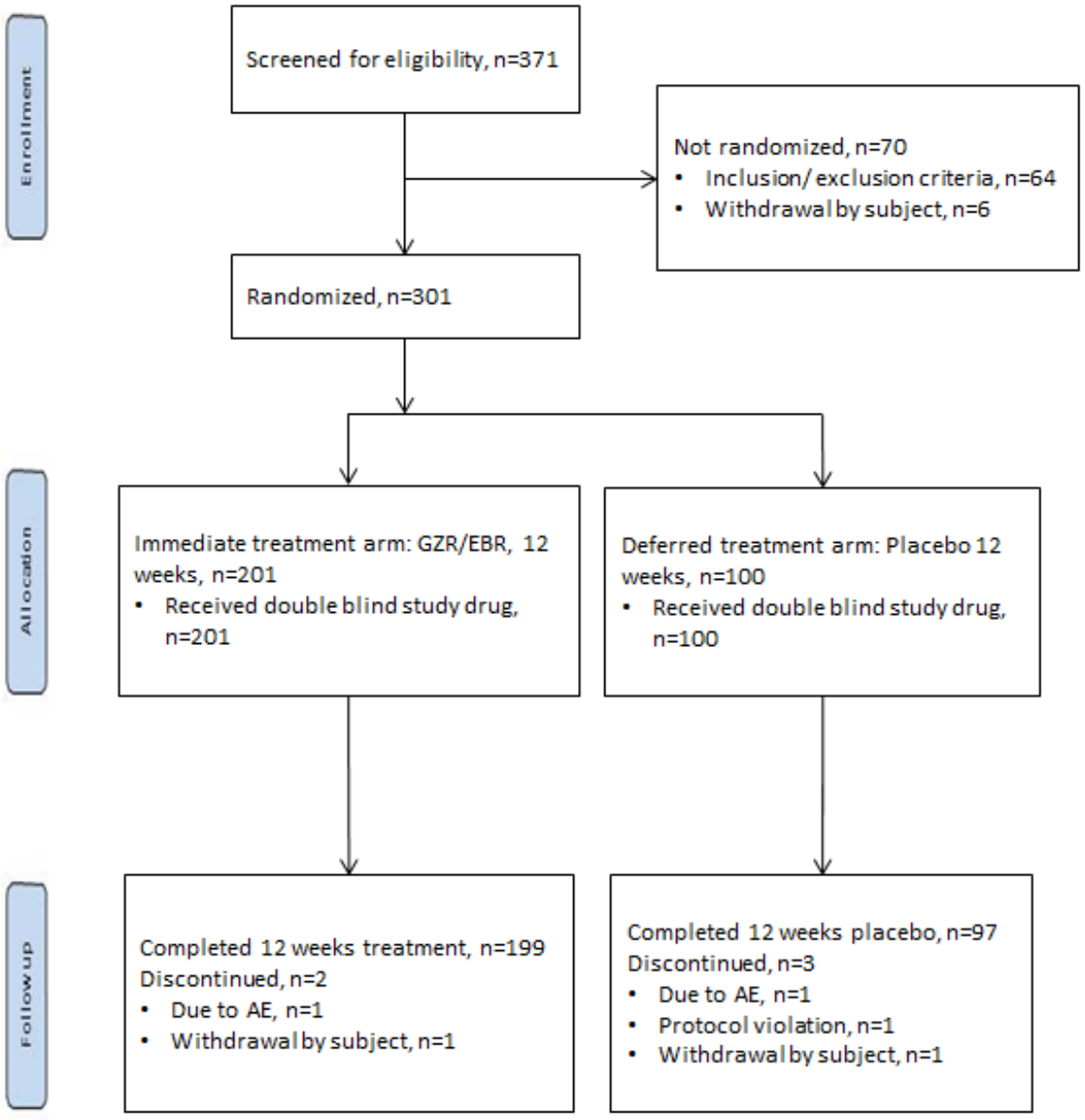


Abbreviations. EBR/GZR, grazoprevir/elbasvir; RBV, ribavirin

C-EDGE CO-STAR Study NCT02105688[63]

Participant enrollment, randomisation, and disposition have been described in Appendix 5. Study disposition is illustrated in Figure 12 below. The authors reported that patients groups were generally balanced between the immediate- and deferred-treatment groups (Appendix 5), and that all patients were in receipt of OST. A summary of patient baseline characteristics is reported in Table 26.

Figure 12. C-EDGE COSTAR - Consort diagram

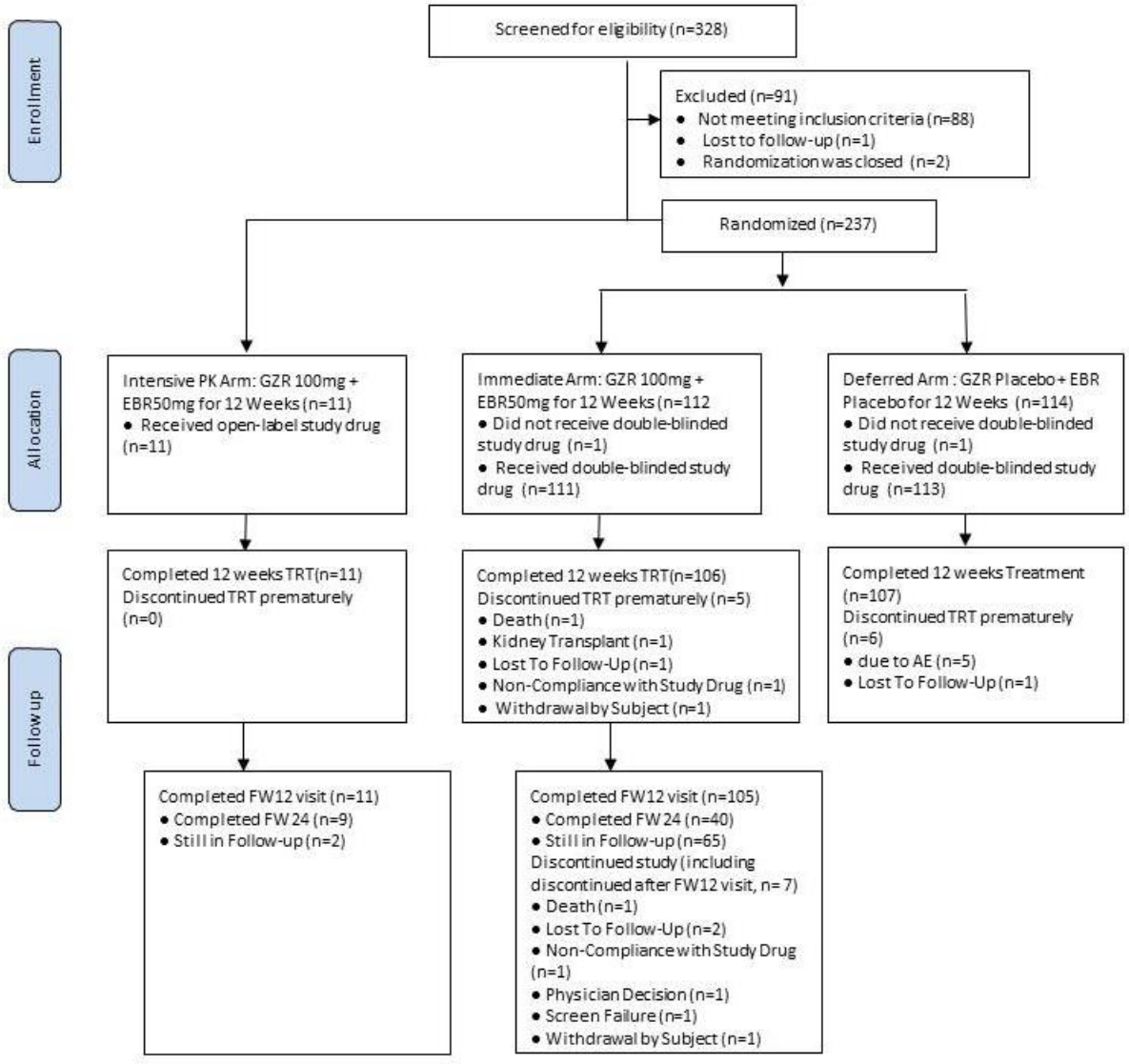


Abbreviations. AE, adverse event; EBR/GZR, grazoprevir/elbasvir

C-SURFER Study NCT02092350[14]

Participant enrollment, randomisation, and disposition have been described in Appendix 5. Study disposition is illustrated in Figure 13 below. Demographic and baseline characteristics were generally balanced between the immediate treatment group, intensive pharmacokinetic, and deferred treatment group (Appendix 5), as can be seen in Table 26 below. Of note, this study enrolled patients with CKD, of which 81.3% were classified as CKD stage 5.

Figure 13. C-SURFER - Consort diagram



Abbreviations. AE, adverse event; CHC, Chronic Hepatitis C; CKD, Chronic Kidney Disease; FW, Follow up Week; EBR/GZR, grazoprevir/elbasvir TRT, Treatment

C-WORTHY Study NCT01717326[61]

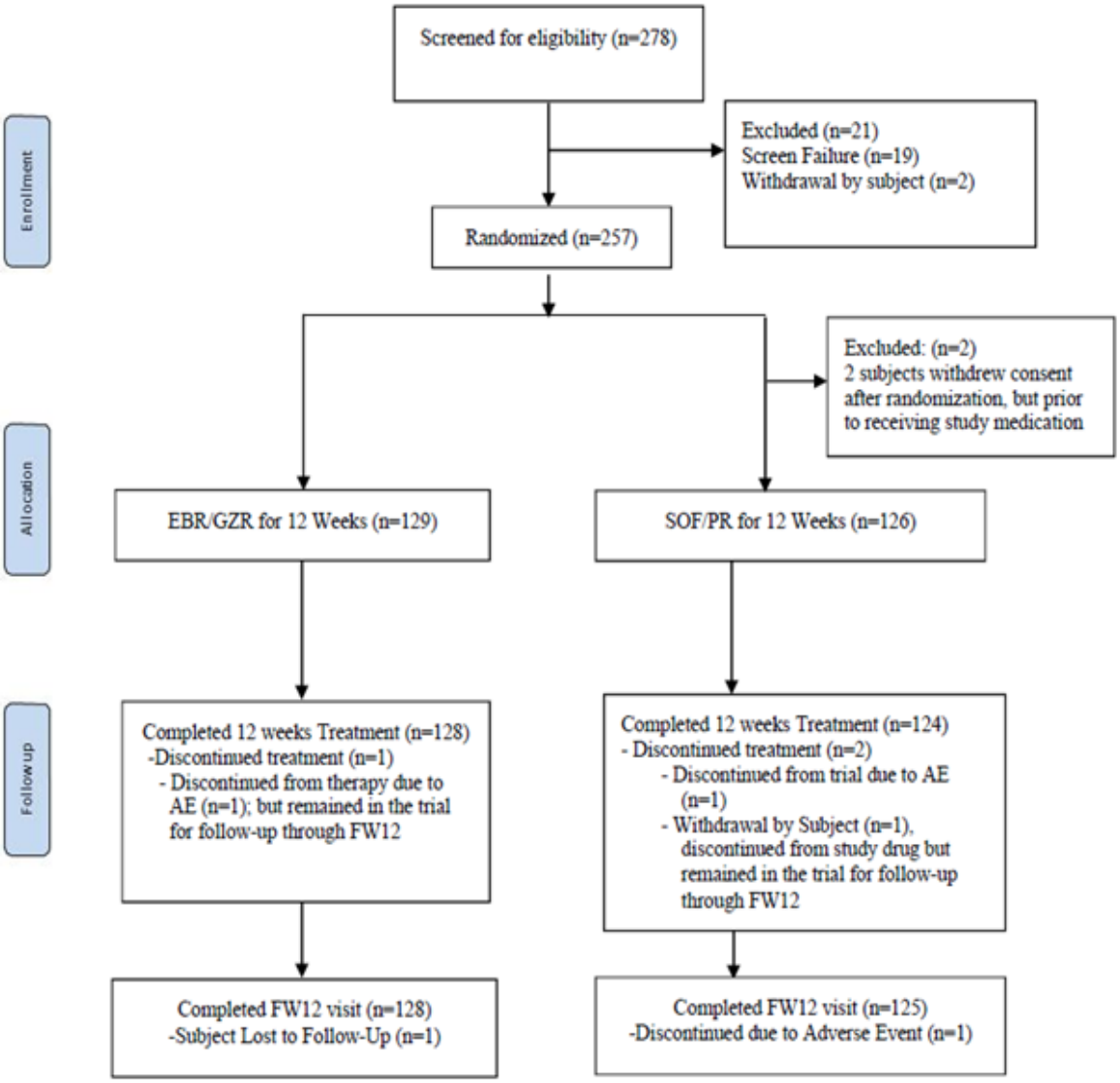
Please note that due to the numerous CONSORT diagrams reported, these are available in Appendix 5. Described below is an overview of patient disposition in the treatment arms of interest. The authors commented that within the respective study parts patient characteristics were generally similar; however, patient characteristics as summarised in Table 26 demonstrate variation across the treatment arms. A descriptive overview of patient baseline characteristics, for the relevant treatment arms per study section is reported in Appendix 5.

- In treatment arm A3, no patient discontinued treatment or discontinued from the study. A total of 31 patients were included in the PP analysis for the primary endpoint.
- In treatment arm B3, no patient discontinued treatment or discontinued from the study. A total of 31 patients were included in the PP analysis for the primary endpoint.
- In treatment arm B5, no patient discontinued treatment or discontinued from the study. A total of 29 patients were included in the PP analysis for the primary endpoint.
- In treatment arm B9, no patient discontinued treatment or discontinued from the study. A total of 33 patients were included in the PP analysis for the primary endpoint.
- In treatment arm B13, a total of three patients discontinued treatment (lost to follow-up n=1, lack of efficacy n=3), the same three patients were reported to have discontinued the study (lost to follow-up n=2, withdrew n=1). Therefore, a total of 28 patients were included in the PP analysis for the primary endpoint.

C-EDGE H2H Study NCT02358044[64]

Participant enrollment, randomisation, and disposition have been described in Appendix 5. Study disposition is illustrated in Figure 14. The CSR reports that the two treatment groups were generally well balanced (Table 26, Appendix 5). Of note, the majority of patients were infected with GT1b (82%) and although eligible for study inclusion no patients with GT6 infection were enrolled.

Figure 14. C-EDGE H2H - Consort diagram



Abbreviations. AE, adverse event; EBR/GZR; elbasvir/grazoprevir; FW, follow-up week; SOF/PR, sofosbuvir +PR

4.5.2 Characteristics of participants at baseline for each trial

Table 26. Summary of baseline characteristics according to published CSRs as per the anticipated EMA license.

C-EDGE TN[59]	EBR/GZR 12 weeks Immediate treatment group N=316	EBR/GZR 12 weeks Deferred treatment group N=105	N/A	NA	N/A
Age,					
Mean (SD)	52.2 (11.1)	53.8 (11.2)	-	-	-
Median (range)	54 (20-78)	55 (22-76)	-	-	-
Gender, n (%)					
Male	171 (54)	56 (53)	-	-	-
Female	145 (46)	49 (47)	-	-	-
Race, n (%)					
White	191 (60)	73 (70)	-	-	-
Black	59 (19)	18 (17)	-	-	-
Asian	54 (17)	13 (12)	-	-	-
Other…	12 (4)	1 (1)	-	-	-
HCV genotype, n (%)					
GT1a	157 (50)	54 (51)	-	-	-
GT1b	131 (42)	40 (38)	-	-	-
GT4	18 (6)	8 (8)	-	-	-
GT6	10 (3)	3 (3)	-	-	-
IL28B CC genotype, n (%)	106 (34)	37 (35)	-	-	-
IL28B non-CC genotype, n (%)	208 (66)	67 (64)	-	-	-
HCV baseline severity, n (%)					
≤ 800 000 IU/mL	94 (30)	39 (37)	-	-	-
> 800 000 IU/mL	222 (70)	66 (63)	-	-	-
Fibrosis status, n (%)					
F0-F2	210 (67)	69 (66)	-	-	-
F3	36 (11)	14 (13)	-	-	-
F4	70 (22)	22 (21)	-	-	-
Treatment history, n (%)					
Naïve	316 (100)	105 (100)	-	-	-

C-EDGE TE[60]	**EBR/GZR 12 weeks N=105**	**N/A**	**N/A**	**NA**	**N/A**
Age,					
Mean (SD)	55.71 (SD 9.81)	-	-	-	-
Gender, n (%)					
Male	66 (62.9)	-	-	-	-
Female	39 (37.1)	-	-	-	-
Race, n (%)					
White	66 (62.9)	-	-	-	-
African American	23 (21.9)	-	-	-	-
Asian	15 (14.3)	-	-	-	-
Other…	1(1.0)	-	-	-	-
HCV genotype, n (%)					
GT1a	61 (58.1)	-	-	-	-
GT1b	34 (32.4)	-	-	-	-
GT1 other	1 (1.0)	-	-	-	-
IL28B CC genotype, n (%)	20 (19.0)[§]	-	-	-	-
IL28B non-CC genotype, n (%)	84 (80.0)[§]	-	-	-	-
Baseline HCV (log10 IU/ml),					
Mean (SD)	6.29 (0.53)	-	-	-	-
Fibrosis status, n (%)					
F0-F2	49 (46.7)	-	-	-	-
F3	19 (18.1)	-	-	-	-
F4	37 (35.2)	-	-	-	-
Treatment history, n (%)					
Naïve		-	-	-	-
Experienced	105 (100)	-	-	-	-
Interferon containing regimen (i.e. IFN/IFN+R)	105 (100)	-	-	-	-
Previous virological response, n (%)					
Null response	49 (46.7)	-	-	-	-
Partial response	21 (20.0)	-	-	-	-
Relapse	35 (33.3)	-	-	-	-

C-SCAPE[62]	C-SCAPE[¶] EBR/GZR 12 weeks N=19	N/A	N/A	N/A	N/A
Age,					
Mean (SD)	52.8 (12.3)	-	-	-	-
Median (range)	49 (34-80)	-	-	-	-
Gender, n (%)					
Male	12 (63.2)	-	-	-	-
Female	7 (36.8)	-	-	-	-
Race, n (%)					
White	13 (68.4)	-	-	-	-
African American	1 (5.3)	-	-	-	-
Asian	5 (26.3)	-	-	-	-
Other…	NA	-	-	-	-
HCV genotype, n (%)					
GT1 overall	1 (5.3)	-	-	-	-
GT1a	NA	-	-	-	-
GT1b	NA	-	-	-	-
GT1 other	NA	-	-	-	-
GT4	10 (52.6)	-	-	-	-
GT5	4 (21.1)	-	-	-	-
GT6	4 (21.1)	-	-	-	-
IL28B CC genotype, n (%)	6 (31.6)	-	-	-	-
IL28B non-CC genotype, n (%)	13 (68.4)	-	-	-	-
HCV baseline severity, n (%)					
≤ 800 000 IU/mL	5 (26.3)	-	-	-	-
> 800 000 IU/mL	14 (73.7)	-	-	-	-
Baseline HCV (log10 IU/ml),					
Mean (SD)	6.4 (0.6)	-	-	-	-
Fibrosis status, n (%)					
F0-F2	17 (89.5)	-	-	-	-
F3	1 (5.3)	-	-	-	-
Treatment history, n (%)					
Naïve	19 (100)	-	-	-	-

C-EDGE COSTAR[63]	EBR/GZR 12 weeks N=201	Placebo weeks N=100	N/A	N/A	N/A
Age,					
Mean (SD)	47.4 (9.9)	46.4 (9.9)	-	-	-
Median (range)	48 (23-66)	47 (24-64)	-	-	-
Gender, n (%)					
Male	153 (76.1)	77 (77.0)	-	-	-
Female	48 (23.9)	23 (23.0)	-	-	-
Race, n (%)					
White	158 (78.6)	84 (84.0)	-	-	-
African American	31 (15.4)	7 (7.0)	-	-	-
Asian	9 (4.5)	7 (7.0)	-	-	-
Other…	3 (1.5)	2 (2.0)	-	-	-
HCV genotype, n (%)					
GT1a	153 (76.1)	75 (75.0)	-	-	-
GT1b	30 (14.9)	15 (15.0)	-	-	-
GT4	12 (6.0)	6 (6.0)	-	-	-
GT6	5 (2.5)	4 (4.0)	-	-	-
IL28B CC genotype, n (%)	57 (28.4)	29 (29.0)	-	-	-
IL28B non-CC genotype, n (%)	141 (70.1)	67 (67.0)	-	-	-
Baseline HCV (log10 IU/ml),					
Mean (SD)	6.63 (6.74)	6.54 (6.63)	-	-	-
Fibrosis status, n (%)					
F0-F2	147 (73.1)	65 (65.0)	-	-	-
F3	14 (7.0)	13 (13.0)	-	-	-
F4	40 (19.9)	20 (20.0)	-	-	-
Special populations, n (%)					
Opiate substitution therapy	201 (100)	100 (100)	-	-	-
Treatment history, n (%)					
Naïve	201 (100)	100 (100)	-	-	-

C-SURFER[14]	EBR/GZR 12 weeks Immediate treatment group N=111	EBR/GZR 12 weeks Deferred treatment group N=113	EBR/GZR* 12 weeks PK treatment group N=11	NA	NA
Age years,					
Mean (SD)	56.5 (9.1)	55.2 (10.1)	58.2 (6.8)	-	-
Gender, n (%)					
Male	81 (73.0)	80 (70.8)	11 (100)	-	-
Female	30 (27.0)	33 (29.2)	0	-	-
Race, n (%)					
White	55 (49.5)	48 (42.5)	6 (54.5)	-	-
Black	50 (45.0)	53 (46.9)	5 (45.5)	-	-
Asian	5 (4.5)	9 (8.0)	0	-	-
Other…	1 (0.9)	3 (2.7)	0	-	-
HCV genotype, n (%)					
GT1a	53 (47.7)	59 (52.2)	10 (90.9)	-	-
GT1b	58 (52.3)	53 (46.9)	1 (9.1)	-	-
GT1 other	0	1 (0.9)	0	-	-
IL28B CC genotype, n (%)	30 (27.0)	30 (26.5)	2 (18.2)	-	-
IL28B non-CC genotype, n (%)	79 (71.2)	83 (73.5)	9 (81.8)	-	-
HCV baseline severity, n (%)					
≤ 800 000 IU/mL	50 (45.0)	47 (41.6)	3 (27.3)	-	-
> 800 000 IU/mL	61 (55.0)	66 (58.4)	8 (72.7)	-	-
Fibrosis status, n (%)					
Cirrhotic	7 (6.2)	7 (6.2)	0	-	-
Non-cirrhotic	104 (93.7)	106 (93.8)	11 (100)	-	-
F0-F2	76 (68.5)	76 (67.3)	11 (100)	-	-
F3	13 (11.7)	15 (13.3)	0	-	-
F4	7 (6.3)	7 (6.2)	0	-	-
Other	15 (13.5)†	15 (13.3)†	0	-	-
Special populations, n (%)					
CKD Stage 4	18 (16.2)	22 (19.5)	4 (36.4)	-	-
CKD Stage 5	93 (83.8)	91 (80.5)	7 (63.6)	-	-
On dialysis	86 (77.5)	87 (77.0)	6 (54.5)	-	-
Not on dialysis	25 (22.5)	26 (23.0)	5 (45.5)	-	-
Diabetes	38 (34.2)	36 (31.9)	6 (54.5)	-	-
No diabetes	73 (65.8)	77 (68.1)	5 (45.5)	-	-

Treatment history, n (%)					
Naïve	91 (82.0)	88 (77.9)	10 (90.9)	-	-
Experienced	20 (18.0)	25 (22.1)	1 (9.1)	-	-
C-WORTHY[61]	**EBR/GZR 12 weeks Arm A3 N=13**	**EBR/GZR 12 weeks Arm B3 N=31**	**EBR/GZR 12 weeks Arm B5 N=29**	**EBR/GZR 12 weeks Arm B9 N=33**	**EBR/GZR 12 weeks Arm B13 N=30**
Age,					
Mean (SD)	43.3 (13.5)	53.6 (8.4)	59.0 (7.8)	54.4 (9.1)	43.5 (10.4)
Gender, n (%)					
Male	7 (53.8)	16 (51.6)	19 (65.5)	20 (60.6)	24 (80.0)
Female	6 (42.6)	15 (48.4)	10 (34.5)	13 (39.4)	6 (20.0)
Race, n (%)					
White	9 (69.2)	27 (87.1)	28 (96.6)	32 (97.0)	24 (80.0)
African American	3 (23.1)	2 (6.5)	1 (3.4)	1 (3.0)	4 (13.3)
Asian	1 (7.7)	2 (6.5)	NR	NR	1 (3.3)
Other…	NR	NR	NR	NR	1 (3.3)
HCV genotype, n (%)					
GT1a		30 (96.8)	20 (69.0)	19 (57.6)	22 (73.3)
GT1b	13 (100)	1 (3.2)	7 (24.1)	14 (42.4)	8 (26.7)
GT1 other			2 (6.9)		
IL28B CC genotype, n (%)	2 (15.4)	6 (19.4)	10 (34.5)	1 (3.0)	8 (26.7)
IL28B non-CC genotype, n (%)	11 (84.6)	25 (80.6)	19 (65.5)	32 (97.0)	22 (73.3)
Baseline HCV (log10 IU/ml),					
Mean (SD)	6.45 (6.51)	6.78 (6.83)	6.69 (6.71)	6.85 (6.79)	6.96 (7.22)
Fibrosis status, n (%)					
F0-F2	13 (100)	26 (83.9)	NR	16 (48.5)	27 (90.0)
F3	NR	5 (16.1)	NR	3 (9.1)	3 (10.0)
F4	NR	NR	29 (100)	14 (42.4)	NR
Treatment history, n (%)					
Naïve	13 (100)	31 (100)	29 (100)	NR	NR
Experienced	NR	NR	NR	33 (100)	30 (100)
Previous virological response, n (%)					
Null response	NR	NR	NR	33 (100)	NR
Special populations, n (%)					
HIV positive	NR	NR	NR	NR	30 (100)

C-EDGE H2H[64]	EBR/GZR 12 weeks N=129	SOF+PR 12 weeks N=126	NA	NA	NA
Age,					
Mean (SD)	47.6 (12.4)	48.2 (12.4)	-	-	-
Median (range)	49 (21-68)	49 (22-76)	-	-	-
Gender, n (%)					
Male	55 (42.6)	62 (49.2)	-	-	-
Female	74 (57.4)	64 (50.8)	-	-	-
Race, n (%)					
White	128 (99.2)	125 (99.2)	-	-	-
Asian	1 (0.8)	1 (0.8)	-	-	-
HCV genotype, n (%)					
GT1a	18 (14.0)	17 (13.5)	-	-	-
GT1b	105 (81.4)	104 (82.5)	-	-	-
GT4	6 (4.7)	5 (4.0)	-	-	-
IL28B CC genotype, n (%)	26 (20.2)	26 (20.6)	-	-	-
IL28B non-CC genotype, n (%)**	100 (77.5)	98 (77.8)	-	-	-
HCV baseline severity, n (%)					
≤ 800 000 IU/mL	39 (30.2)	45 (35.7)	-	-	-
> 800 000 IU/mL	90 (69.8)	81 (64.3)	-	-	-
Baseline HCV (log10 IU/ml),					
Mean (SD)	6.44 (6.50)	6.46 (6.75)	-	-	-
Fibrosis status, n (%)††			-	-	-
F0-F2	97 (75.2)	92 (73.0)	-	-	-
F3	9 (7.0)	13 (10.3)	-	-	-
F4	22 (17.1)	21 (16.7)	-	-	-
Treatment history, n (%)					
Naïve	100 (77.5)	91 (72.2)	-	-	-
Experienced	29 (22.5)	35 (27.8)	-	-	-
Previous virological response, n (%)					
PEG+RBV Null response	11 (8.5)	14 (11.1)	-	-	-
PEG+RBV Partial response	6 (4.7)	8 (6.3)	-	-	-
PEG+RBV Relapser	12 (9.3)	13 (10.3)	-	-	-

Abbreviation: CKD, chronic kidney disease; DAA, direct acting antiviral; EBR/GZR, grazoprevir/elbasvir; HCV, hepatitis C virus; IFN, interferon;
*Non-randomised treatment group; †Other category applies to 30 patients assessed by Fibrotest but could not be considered cirrhotic; § One patient n=1/105, did not have data and was considered as missing for IL28B GT; ¶ C-SCAPE reported that one patient did not have a documented fibrosis score.; **3 patients in the EBR/GZR arm had IL28B GT data missing, and 2 patients in the SOF+PR arm had IL28B GT data missing; †† 1 patient in the EBR/GZR treatment arm did not have a fibrosis stage score

4.6 *Quality assessment of the relevant randomised controlled trials*

A description of the Cochrane Risk of bias quality assessment tool and risk of bias assessment for all included studies has been presented in Appendix 6. Table 27 below summarises the quality assessment of RCTs for EBR/GZR trials only.

Table 27. Summary of quality assessment for trials reporting EBR/GZR

Trial	C-EDGE CO-STAR MSD CSR 2015 [63]	C-EDGE TE MSD CSR 2015 [60]	C-EDGE TN MSD CSR 2015 [59]	C-SCAPE MSD CSR 2015 [62]	C-SURFER MSD CSR 2015 [14]	C-WORTHY MSD CSR 2015 [61]	C-EDGE H2H MSD CSR 2016 [64]
Selection bias (Random sequence generation)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Selection bias (Allocation concealment)	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Performance bias	Low risk	High risk	Low risk	High risk	Low risk	Unclear risk	High risk
Detection bias	Low risk	High risk	Low risk	High risk	Low risk	Unclear risk	High risk
Attrition bias	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Reporting bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Other bias	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk

Risk of Bias instrument, endorsed by the Cochrane Collaboration (Appendix 6).

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

Below are clinical effectiveness results according to the primary objective (SVR12) for each of the included EBR/GZR RCTs (n=7) as relevant to the anticipated EMA label and the context of this submission, i.e. the treatment of patients with chronic HCV GT1a, GT1b, and GT4 infections treated with EBR/GZR for 12 weeks split according to treatment experience and cirrhosis stage, where available from the CSR. The post-hoc analysis used to facilitate NMA and the health economic model reported in section 4.10

C-EDGE TN Study, NCT02105467[59]

Primary endpoint

The primary endpoint, SVR12, was reported using the FAS (n=316), and has been summarised in Table 28. The overall SVR12 rate for GT1, GT4, and GT6 was 94.6% (95% CI, 91.5%-96.8%) for patients randomised to the immediate treatment group (n=299/316). The SVR12 rate for GT1a, GT1b, and GT4 infection, irrespective of treatment experience or cirrhosis stage is reported in Table 28. The pooled SVR12 for patients with GT1, GT4, and GT6 infections was 97% (95%CI, 90%-100%) for patients with cirrhosis, and 94% (95%CI, 90%-97%) in patients without cirrhosis.

Table 28. C-EDGE TN, SVR12 results for patients treated with EBR/GZR for 12 weeks

Treatment outcome	Treatment regimen: EBR/GZR 12 weeks		
	n/N	%	95% CI
Primary endpoint			
SVR 12*, FAS GT1, GT4, and GT6 TN, C or NC	299/316	94.6	91.5-96.8¶
GT1a, FAS TN, C or NC	144/157	91.7	86.3-95.5
GT1b, FAS TN, C or NC	129/131	98.5	94.6-99.8
GT4, FAS TN, C or NC	18/18	100	81.5-100

Abbreviations. C, cirrhotic; CI, confidence interval; FAS, full analysis set; EBR/GZR, grazoprevir/elbasvir; NC, non-cirrhotic; SVR, sustained virologic response; TN, treatment naïve;
* LLoQ=lower limit of quantification (HCV RNA is detected but <15 IU/mL);
† One patient was missing baseline IL28B genotype data
¶ p=<0.001, based on a one-sided exact test for a binomial proportion. A one-sided p-value<0.025 supports a conclusion that the true SVR12 is >73%.

C-EDGE TE Study NCT02105701[60]

Primary endpoint

The primary endpoint, SVR12, was reported using the FAS (n=105). The SVR12 was 92.4% (n=97/105) 95% CI 85.5-96.7) p<0.001 compared with the historical control of 58%.

Presented in Table 29 are the results for the primary endpoint, SVR12 in patients described as predominantly GT1 (population split: GT1a 58.1%, GT1b 32.4%, and GT4 8.6%) who had previously failed therapy with PR treatment.

Table 29. C-EDGE TE, SVR12 results for patients treated with EBR/GZR for 12 weeks.

Treatment outcome	Treatment regimen: EBR/GZR 12 weeks		
	n/N	%	95% CI
Primary endpoint			
SVR12, FAS GT1 (1a, 1b) and GT4 TE	97/105	92.4	85.5-96.7 p<0.001*
SVR12 FAS GT1a TE	55/61	90.2	NR
SVR12 FAS GT1b TE	34/34	100.0	NR
SVR12 FAS GT4 TE	7/9	77.8	NR

Abbreviations; CI, confidence interval; mFAS, modified full analysis set; GT, genotype; EBR/GZR, grazoprevir/elbasvir; PR, pegylated interferon+ribavirin; SVR, sustained virologic response, TE, treatment experienced
* Based on a one-sided exact test for binomial proportion. A one-sided p-value <0.0125 support a conclusion that the SVR12 is >58%

C-SCAPE Study NCT01932762[62]

Primary endpoint

A total of 19 patients were randomised to treatment arm B3, of interest. A total of 6 patients were excluded from the PP analysis due to protocol violation, this included: mixed GT infection (n=2), use of prohibited medication (n=2), use of medication outside the protocol allowance (n=1), and loss to follow up (n=1). The SVR12 for treatment arm B3 was 76.9% (95% CI, 46.2-95.0%) (n=10/13); however, this included patients with GT5 and GT6 infections, not relevant to this submission. The SVR12 for patients with GT4 infection was 100% (95% CI, 59.0-100%) (n=7/7).

Table 30. C-SCAPE, SVR12 results for patients treated with EBR/GZR for 12 weeks (treatment arm B3)

Treatment outcome	Treatment regimen: EBR/GZR 12 weeks Treatment arm B3		
	n/N	%	95% CI
Primary endpoint			
SVR12, PP Overall GT4, GT5, and GT6 TN NC	10/13	76.9	46.2-95.0
SVR12 PP GT4 TN NC	7/7	100	59.0-100

Abbreviations; CI, confidence interval EBR/GZR, grazoprevir/elbasvir; GT, genotype; NC, non-cirrhotic; TN, treatment naïve; PP, per protocol population

C-EDGE CO-STAR Study NCT02105688[63]

Primary endpoint

A total of 301 patients randomised to the immediate (n=201) or deferred treatment arms (n=100) received EBR/GZR for 12 weeks. The primary endpoint, SVR12, was reported using the mFAS in the immediate treatment group (n=198).The overall SVR12 rate irrespective of GT was 95.5% (95% CI; 91.5-97.9) p<0.001, demonstrating a statistically significant difference compared with the historical control SVR12 rate of 67% and supporting a conclusion that SVR12 is >67%. The SVR12 rate per genotype is described in Table 31; this is not split according to cirrhosis stage. It is of note that five patients from the mFAS (n=189) who achieved a SVR for their primary infection experienced re-infection as assessed by population sequencing and phylogenetic analysis.

Table 31. C-EDGE CO-STAR, SVR12 results for patients treated with EBR/GZR for 12 weeks (immediate treatment arm)

Treatment outcome	Treatment regimen: EBR/GZR 12 weeks Immediate treatment arm		
	n/N	%	95% CI
Primary endpoint			
SVR 12, mFAS Overall GT1, GT4, and GT6	189/198	95.5	91.5-97.9 p<0.001
SVR 12, mFAS* GT1a overall	146/152	96.1	NR
SVR 12, mFAS* GT1b overall	28/29	96.6	NR
SVR12, mFAS* GT 4 overall	11/11	100	NR

Abbreviations. GT, genotype, EBR/GZR, grazoprevir/elbasvir; mFAS, modified full analysis set; SVR, sustained virologic response;
*efficacy relates to the number of patients achieving SVR12 in respective GT subgroups using the mFAS.

C-SURFER Study NCT02092350[14]

Primary endpoint

The primary endpoint, SVR12, was reported using the mFAS (n=116), which combined the immediate- and intensive PK- treatment groups (Table 32). The SVR12 rate was 99.1% (95% CI; 95.3-100%, n=115/116) in the combined treatment group, and was statistically significant compared with the SVR12 45% historical control rate (p<0.001).

Table 32. C-SURFER, SVR12 results for patients treated with EBR/GZR for 12 weeks

Treatment outcome	Treatment regimen: EBR/GZR 12 weeks GT1 population overall		
	n/N	%	95% CI
Primary endpoint			
SVR 12*, mFAS TN or TE, C or NC	115/116	99.1	95.3-100

Abbreviations. C, cirrhotic; FAS, full analysis set; mFAS, modified full analysis set; NC, non-cirrhotic; TE, treatment experienced; TE, treatment naïve
*LLoQ=lower limit of quantification (HCV RNA is detected but <15 IU/mL)

C-WORTHY Study NCT01717326[61]

Primary endpoint

A total of 136 patients were randomised to the treatment arms of interest, and received EBR/GZR for 12 weeks. The primary endpoint, SVR12, was reported using the PP population as defined in section 4.4.1. The results are summarised in Table 33.

SVR12 was 100% (95% CI 73.5-100%) and 96.8% (95% CI 83.3-99.9%) in treatment arms A3 and B3, respectively (Table 33). All patients in treatment arm A3 reported GT1b infections, and one patient from treatment arm B3 had GT1b infection and achieved SVR12. Of the 30 patients in treatment arm B3 with GT1a infection, 96.7% (n=29/30) achieved SVR12. The CSR reports that the pooled (treatment arm A3 and B3) SVR12 rate was 97.7% (n=42/43) in the PP population; this represents GT1 infection overall for patients described as treatment naïve non-cirrhotic.

In treatment arm B13, HCV/HIV co-infected patients, SVR12 was 92.9% (95% CI 76.5-99.1%) (n=26/28) in the primary PP population. In treatment arm B5, TN C patients, SVR12 was 96.6% (95% CI 82.2-99.9%) (n=28/29). Treatment arm B9 reported SVR12 at 90.9% (95% CI 75.7-98.1%) (n=30/33) in hard-to-cure patients defined as TE prior null responders (prior PR treatment) of which ~40% were cirrhotic.

Table 33. C-WORTHY, SVR12 results for patients treated with EBR/GZR for 12 weeks.

Treatment arm	Treatment regimen: EBR/GZR (12 weeks) GT1 patients overall		
	n/N	%	95% CI*
Primary endpoint SVR 12 per protocol population			
A3 TN, NC, GT1b	12/12	100	73.5-100
B3[†] TN, NC, GT1a	30/31	96.8	83.3-99.9
B5 TN, C, GT1a or GT1b	28/29	96.6	82.2-99.9
B9 TE, C or NC, GT1a or GT1b	30/33	90.9	75.7-98.1
B13 HIV co-infected only TN, NC, GT1a or GT1b	26/28	92.9	76.5-99.1

Abbreviations. C, cirrhotic; CI, confidence interval; GT, genotype; EBR/GZR, grazoprevir/elbasvir; NC, non-cirrhotic; SVR, sustained virologic response; TE, treatment experienced; TN, treatment naïve
*Clopper-Pearson method
[†]One treatment-naïve, non-cirrhotic, mono-infected patient with HCV genotype 1b was allocated to the B3 regimen for genotype 1a patients.

C-EDGE H2H Study NCT02358044[64]

Primary endpoint

A total of 255 patients were randomised to EBR/GZR or SOF+PR for 12 weeks. The primary endpoint, SVR12, was reported using the FAS population as defined in section 4.4.1. The results summarised in Table 34 are irrespective of GT; SVR12 was 99.2% (n=128/129) and 90.5% (n=114/126) for the EBR/GZR and SOF+PR treatment arms, respectively. The estimated adjusted difference between the two treatment groups was 8.8% (95% CI, 3.6%-15.3%). As the lower bound of the one-sided one-sample exact test was greater than -10%, the non-inferiority of EBR/GZR compared with SOF+PR was established. As stated within the CSR, the superiority (secondary objective) of EBR/GZR compared with SOF+PR was also established (not reported here). The authors commented that the efficacy estimates for EBR/GZR and SOF+PR were comparable among GT1a infected patients, whereas the observed efficacy of EBR/GZR was higher than SOF+PR in patients with GT1b infection; these values are summarised in Table 34.

Table 34. C-EDGE H2H, SVR12 results for patients treated with EBR/GZR or SOF+PR for 12 weeks.

Treatment arm	Primary endpoint SVR 12 per protocol population				
	n/N	%	Unadjusted difference in %	Adjusted difference in % (95%CI)*	P value†
EBR/GZR, 12 weeks GT1 and GT4 FAS population	128/129	99.2	8.7	8.8 (3.6-15.3)	<0.001
SOF+PR, 12 weeks GT1 and 4 FAS population	114/126	90.5			
EBR/GZR, 12 weeks GT1a FAS population	18/18	100	0.0 (-18.0-18.9)	NA	NA
SOF+PR, 12 weeks GT1a FAS population	17/17	100			
EBR/GZR, 12 weeks GT1b FAS population	104/105	99	8.7 (3.2-16.0)	NA	NA
SOF+PR, 12 weeks GT1b FAS population	94/104	90.4			
EBR/GZR, 12 weeks GT4 FAS population	6/6	100	40 (-10.9-78.1)	NA	NA
SOF+PR, 12 weeks GT4 FAS population	3/5	60			

Abbreviations. FAS, full analysis set, EBR/GZR, grazoprevir/elbasvir; SOF+PR, sofosbuvir/peg-IFN+RBV; SVR, sustained virologic response

*Based on stratified Miettinen & Nurminen method adjusted for genotype (1a vs. non-1a) and fibrosis stage (cirrhotic vs. non-cirrhotic)

†The lower bound of 95% CI will be compared to pre-specified non-inferiority margin, -10% to evaluate non-inferiority

4.8 Subgroup analysis

MSD is presenting post-hoc analysis of the included CSRs to support the NMA and health economic model as previously described.

4.9 Meta-analysis

As C-EDGE H2H was the only head-to-head trial featuring EBR/GZR, a traditional pairwise meta-analysis was not carried out. However, in an evidence network where both direct and indirect evidence exists, it is informative to perform a meta-analysis of the relative treatment effects based on only the direct evidence before performing the NMA where direct and indirect evidence is combined. Although such analyses can be performed by repeatedly performing traditional pairwise meta-analysis for each direct comparison, a more efficient approach is the use of independent-means models where pooled estimates for all direct comparisons are simultaneously obtained[72]. The findings of a synthesis of direct evidence

will improve the understanding of the findings of the NMA where direct and indirect evidence are combined.

4.10 *Indirect and mixed treatment comparisons*

4.10.1 Search strategy

Please see section 4.1-4.16 for full details relating to SLR methodology. The SLR search methodology is identical for both EBR/GZR and comparator technologies.

4.10.2 Details of treatments

As per the final scope all relevant comparators have been included in the NMA. The analyses are presented according to current NICE recommendations, i.e. intervention split by GT, prior treatment experience, and cirrhosis status. The comparators of relevance to the decision problem are:

- **GT1a/GT1b**: LDV/SOF, SOF+PR, PR, 3D (OMB +PAR/r+DAS) +/- RBV, and DCV+SOF.
- **GT4:** LDV/SOF, SOF+PR, PR, 2D (OMB+PAR/r), and DCV+PR.

4.10.3 Criteria used in trial selection

As per section 4.1.3 trial selection was decided according to hierarchical exclusion criteria (Table 20). Included trials were then reviewed for comparators that have been recommended by NICE. Publications related to these trials were then checked to see whether they contained information on outcomes for subgroups of interest e.g. GT1a, treatment-naïve, without cirrhosis. In the absence of specific subgroup information, assumptions were made to facilitate to comparisons with trials with data available. As reported in Figure 1, 120 citations representing 109 clinical trials were identified; of which, 70 citations were excluded (69 clinical trials). This meant that 50 citations representing 40 clinical trials were included in the NMA (inclusive of EBR/GZR). A list of included/excluded citations can be found in Appendix 3.

4.10.4 Summary of trials

Trials included within the NMA of SVR are presented in Table 35 and Table 36. Trials included within the NMA of safety outcomes can be found in Table 37. Please note that data for the outcomes of interest for EBR/GZR were provided by MSD in the form of post-hoc analysis. All GT1 (GT1a or GT1b) or GT4 patients from the included EBR/GZR CSRs were considered in the post-hoc analyses; no additional inclusion/exclusion criteria were implemented during the post/hoc analyses[73].

4.10.5 Trials identified in search strategy

Trials included in the NMA were those that met the criteria outlined in section 4.1.3 and also presented data for a relevant comparator within a subgroup of interest. From the 40 trials included within the NMA, these were grouped by primary intervention giving 8 for EBR/GZR, 5 for SMV+PR, 5 for SOF+PR, 8 for OMB/PAR/r+DAS+/-RBV, 1 for OMB/PAR/r+RBV, 9 for LDV/SOF, 2 for SOF+DCV, 1 for DCV+PR, finally 1 for TVR+PR that was included to increase the robustness of the network. Most trials were included in both the analysis of SVR and safety, with the exception of ATOMIC, AI444040, ERADICATE, and LONESTAR which only featured in the safety analysis, and ALLY-2 which was only analysed for SVR[73].

Table 35. GT1a/GT1b trials of included interventions for the NMA of SVRs

	Genotype 1a			
	Treatment-naïve		Treatment experienced	
	Cirrhosis	No cirrhosis	Cirrhosis	No cirrhosis
Comparator	**Trials**	**Trials**	**Trials**	**Trials**
EBR/GZR 1-12[73]	C-EDGE TN[59], C-EDGE CO-INFECTION[74], C-SURFER[14], C-WORTHY[61], C-EDGE CO-STAR[63]	C-EDGE TN[59], C-EDGE CO-INFECTION[74], C-SURFER[14], C-WORTHY[61], C-EDGE CO-STAR[63], PN077[64]	C-EDGE TE[60], C-SURFER[14], C-WORTHY[61]	C-EDGE TE[60], C-SURFER[14], C-WORTHY[61], PN077[64]
PR 1-48	QUEST-1[68], QUEST-2[69]	ADVANCE[75], PILLAR[76], QUEST-1[68], QUEST-2[69]	PROMISE[77]	PROMISE[77]
SOF+PR 1-12	Pearlman et al., 2015[78]	PN077[64], Rodriguez-Torres et al., 2015[79]	Pearlman et al., 2015[78]	PN077[64], Pol et al., 2015[80]
SMV+PR 1-12, PR 13-24	QUEST-1[68], QUEST-2[69]	PILLAR[76], QUEST-1[68], QUEST-2[69]	PROMISE[77]	PROMISE[77]
OMB+PAR/r+DAS+R 1-12	Not recommended by NICE	MALACHITE-I[81], PEARL-IV[82], SAPPHIRE-I [83]	Not recommended by NICE	MALACHITE-II[81], SAPPHIRE-II [84]
OMB+PAR/r+DAS+R 1-24	TURQUOISE-II [85]	Not recommended by NICE	TURQUOISE-II[85]	Not recommended by NICE
LDV/SOF 1-8	Not recommended by NICE	ION-3[86]	Not recommended by NICE	Not recommended by NICE
LDV/SOF 1-12	ION-1[87], Lim et al., 2015[88], Mizokami et al., 2015[89], SYNERGY[90-93]	Not recommended by NICE	ELECTRON, ION-2[94], Lim et al., 2015[88], Mizokami et al., 2015[89]	ION-2[94], Lim et al., 2015[88], Mizokami et al., 2015[89], SYNERGY[90-93]
DCV+SOF 1-12	Not recommended by NICE	ALLY-2[95]	Not recommended by NICE	ALLY-2[95]
	Genotype 1b			
	Treatment-naïve		Treatment experienced	
	Cirrhosis	No cirrhosis	Cirrhosis	No cirrhosis
Comparator	**Trials**	**Trials**	**Trials**	**Trials**
EBR/GZR1-12[73]	C-EDGE TN[59], C-EDGE CO-INFECTION[74], C-WORTHY[61], C-EDGE CO-	C-EDGE TN[59], C-EDGE CO-INFECTION[74], C-SURFER[14], C-WORTHY[61], C-	C-EDGE TE[60], C-WORTHY[61], PN077[64]	C-EDGE TE[60], C-SURFER[14], C-WORTHY[61], PN077[64]

	STAR[63], PN077[64]	EDGE CO-STAR[63], PN077[64]		
PR 1-48	QUEST-1[68], QUEST-2[69]	ADVANCE[75], PILLAR[76], QUEST-1[68], QUEST-2[69]	PROMISE[77]	PROMISE[77]
SOF+PR 1-12	PN077[64]	PN077[64], Rodriguez-Torres et al., 2015[79]	PN077[64]	PN077[64], Pol et al., 2015[80]
SMV+PR 1-12, PR 13-24	QUEST-1[68], QUEST-2[69]	PILLAR[76], QUEST-1[68], QUEST-2[69]	PROMISE[77]	PROMISE[77]
OMB+PAR/r+DAS+R 1-12	TURQUOISE-II[85]	Not recommended by NICE	TURQUOISE-II[85]	Not recommended by NICE
OMB+PAR/r+DAS 1-12	Not recommended by NICE	MALACHITE-I[81], PEARL-III[82]	Not recommended by NICE	PEARL-II[96]
LDV/SOF 1-8	Not recommended by NICE	ION-3[86]	Not recommended by NICE	Not recommended by NICE
LDV/SOF 1-12	ION-1[87], Lim et al., 2015[88], Mizokami et al., 2015[89], SYNERGY[90-93]	Not recommended by NICE	ELECTRON [97], ION-2[94], Lim et al., 2015[88], Mizokami et al., 2015[89]	ION-2 [94], Lim et al., 2015[88], Mizokami et al., 2015[89], SYNERGY[90-93]
DCV+SOF 1-12	Not recommended by NICE	ALLY-2[95]	Not recommended by NICE	ALLY-2[95]

Abbreviations. DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR.

Table 36: GT4 trials of included interventions for the NMA of SVRs

	Genotype 4			
	Treatment-naïve		Treatment experienced	
	Cirrhosis	No cirrhosis	Cirrhosis	No cirrhosis
Comparator	**Trials**	**Trials**	**Trials**	**Trials**
EBR/GZR1-12[73]	C-EDGE TN[59], C-EDGE CO-INFECTION[74], PN077[64]	C-EDGE TN[59], C-EDGE CO-INFECTION[74], C-SCAPE[62], PN077[64]	C-EDGE TE[60], PNO77[64]	C-EDGE TE[60], PNO77[64]
PR 1-48	COMMAND-4[98]	COMMAND-4[98]	COMMAND-4[98]	COMMAND-4[98]
SOF+PR 1-12	NEUTRINO[99], Pearlman et al., 2015[78], PN077[64]	Not recommended by NICE	Pearlman et al., 2015[78], PN077[64]	Not recommended by NICE
SMV+PR 1-12, PR 13-24	RESTORE [100]	RESTORE[100]	RESTORE[100]	RESTORE[100]
OMB+PAR/r+R 1-12	Not recommended by NICE	PEARL-I[101, 102]	Not recommended by NICE	PEARL-I[101, 102]
OMB+PAR/r+R 1-24	PEARL-I[101, 102]	Not recommended by NICE	PEARL-I[101, 102]	Not recommended by NICE
LDV/SOF 1-8	Not recommended by NICE			
LDV/SOF 1-12	ION-1[87], Lim et al., 2015[88], Mizokami et al., 2015[89], SYNERGY[90-93]	Not recommended by NICE	ELECTRON[97], ION-2[94], Lim et al., 2015[88], Mizokami et al., 2015[89]	ION-2[94], Lim et al., 2015[88], Mizokami et al., 2015[89], SYNERGY[90-93]
DCV+SOF 1-12	Not recommended by NICE	Not recommended by NICE	Not recommended by NICE	ALLY-2[95]
DCV+PR 1-24	COMMAND-4[98]	COMMAND-4[98]	COMMAND-4[98]	COMMAND-4[98]

Abbreviations. DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR.

Table 37. GT1/GT4 trials of included intervention for the NMA of safety outcomes

	Genotype 1		Genotype 4	
	Cirrhosis	No cirrhosis	Cirrhosis	No cirrhosis
Comparator	**Trials**	**Trials**	**Trials**	**Trials**
EBR/GZR1-12	C-EDGE TN[59], C-EDGE TE[60], C-EDGE CO-INFECTION[74], C-SURFER[14], C-WORTHY[61], C-EDGE CO-STAR[63], PN077[64]	C-EDGE TN[59], C-EDGE TE[60], C-EDGE CO-INFECTION[74], C-SURFER[14], C-WORTHY[61], C-EDGE CO-STAR[63], PN077[64]	C-EDGE TN[59], C-EDGE TE[60], C-EDGE CO-INFECTION[74]	C-EDGE TN[59], C-EDGE TE[60], C-EDGE CO-INFECTION[74], C-SCAPE [62], PN077[64]
PR 1-48	PROMISE[77], QUEST-1[68], QUEST-2[69]	PILLAR[76]	COMMAND-4[98]	COMMAND-4[98]
SOF+PR 1-12	Pearlman et al., 2015 [78], PN077[64]	ATOMIC[103], Pol et al., 2015[80], PN077[64]	Pearlman et al., 2015[78], PN077[64]	Not recommended by NICE
SMV+PR 1-12, PR 13-24	PROMISE [77], QUEST-1[68], QUEST-2[69]	PILLAR [76]	RESTORE [100]	RESTORE[100]
OMB+PAR/r 1-12	Not recommended by NICE	MALACHITE-I[81], PEARL-II[96], PEARL-III[82], PEARL-IV[82]	Not recommended by NICE	Not recommended by NICE
OMB+PAR/r+DAS+R 1-12	TURQUOISE-II[85]	MALACHITE-I[81], MALACHITE-II[81], PEARL-II[96], PEARL-III[82],PEARL-IV[82], SAPPHIRE-I,[83] SAPPHIRE-II[84]	Not recommended by NICE	Not recommended by NICE
OMB+PAR/r+DAS+R 1-24	TURQUOISE-II[85]	Not recommended by NICE	Not recommended by NICE	Not recommended by NICE
OMB+PAR/r+R 1-12	Not recommended by NICE	Not recommended by NICE	Not recommended by NICE	PEARL-I[101, 102]
OMB+PAR/r+R 1-24	Not recommended by NICE	Not recommended by NICE	PEARL-I[101, 102]	Not recommended by NICE
LDV/SOF 1-8	Not recommended by NICE	ION-3[86], LONESTAR[104]	Not recommended by NICE	Not recommended by NICE
LDV/SOF 1-12	ELECTRON[97], ION-1[87], ION-2[94], Lim et al., 2015[88], LONESTAR[104], Mizokami et al., 2015[89], SYNERGY[90-93]	ERADICATE [105], ION-3[86], LONESTAR[104], SYNERGY[90-93]	ELECTRON[97], ION-1[87], ION-2[94], Lim et al., 2015[88], LONESTAR[104], Mizokami et al., 2015[89], SYNERGY[90-93]	ERADICATE[105], ION-3[86], LONESTAR[104], SYNERGY[90-93]
DCV+SOF 1-12	Not recommended by NICE	AI444040[98]	Not recommended by NICE	AI444040[98]
DCV+PR 1-24	Not recommended by NICE	Not recommended by NICE	COMMAND-4[98]	COMMAND-4[98]

Abbreviations. DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR

4.10.6 Rationale for choice of outcome measure chosen

The NMA was designed to provide comparative estimates for EBR/GZR vs. other interventions currently recommended by NICE for patients with HCV for the following outcomes:

1. SVR, defined as the proportion of patients with HCV RNA less than the lower limit of quantification either 12 or 24 weeks after completion of treatment
2. Discontinuation related to AEs (DAE), defined as the proportion of patients who permanently discontinue all study drugs prior to completion of treatment
3. Overall AEs (OAE), defined as the proportion of patients experiencing any type of AE up to 30 days post treatment
4. Anaemia, nausea, neutropenia, pruritus, and rash, defined for each outcome as the proportion of patients experiencing an event up to 30 days post treatment.

    a. Thrombocytopenia was included in the SLR; however, it was not possible to carry out an NMA for thrombocytopenia due to a lack of data from a PR control arm.

These outcomes were selected on the basis that they are the most important influences on clinical decision making[33]. They are also consistent with the outcomes included within previous submissions in this clinical area.

4.10.7 Populations in the included trials

The NMA of SVR was carried out across 12 different subgroups, each representing a different GT or sub-GT, prior treatment history, and cirrhosis status. The choice of these differentiating characteristics was based on their potential for effect modification, even with the all-DAA regimens[33]. The choice of these subgroups was also informed by the final scope received by NICE, facilitating the comparison of EBR/GZR to relevant treatments. For safety outcomes, rates tend to not be influenced by viral or host factors, and the main consideration for choice of therapy is likelihood of achieving an SVR[33]. In contrast, treatment factors are associated with higher rates of AE, for example decreases in haemoglobin are more common in regimens which contain RBV[33]. To allow as much data as possible to be included within the analysis while also accounting for differences in treatment combinations, safety outcomes were analysed according to only GT and cirrhosis status.

Data matching these specific subgroups were used wherever available, although this was not possible in all circumstances. Details of the various assumptions that were made for missing data can be found in Section 4.10.8.

4.10.8 Apparent or potential differences in patient populations between the trials

As discussed above, the NMA was conducted on groups with clearly defined characteristics. In all but a handful of included trials, these groups were a subgroup within the population of the trial or arm overall. This meant it was not possible to accurately compare the patient characteristics across these specific subgroups, as information was generally only presented at the arm level. Nonetheless, patient characteristics of included arms were plotted to check for any extreme outliers that might be removed as part of a sensitivity analysis. Details of these sensitivity analyses are included in Section 4.10.15.

Due to subgroup information not being presented in all trials, a number of assumptions had to be made to allow for comparisons to be made.

In GT1, no trials including PR 1-48, SMV+PR 1-12, PR 13-24, or LDV/SOF 1-12 presented SVR data differentiated by sub-GT and cirrhosis status. Therefore, the data for the latter subgroup was used, based on the assumption that it was likely to be a more important effect modifier for these treatments than sub-GT. It is acknowledged that for the SMV+PR 1-12 and PR13-24, SVR estimates include GT1a patients with the Q80k polymorphism, the presence of which has been shown to significantly reduce SVRs associated with SMV treatment. Although these patients are not likely to receive this regimen in clinical practice, and therefore the SVR estimates likely to be lower than expected, they were retained to maintain consistency with the assumptions for other comparators.

In the analysis of safety outcomes, there were no trials of PR 1-48 or SMV+PR 1-12, PR 13-48 conducted exclusively in cirrhotic patients; therefore, effect estimates were use from combined cirrhotic and non-cirrhotic populations. Similarly, there were no trials of DCV+SOF 1-12 conducted entirely in non-cirrhotic populations, so a combined population set was used. One trial of LDV/SOF 1-12 (ELECTRON) was carried out in patients with cirrhosis only; however, this was made up of just 10 patients. Thus, to limit the effect of bias, due to small patient numbers, combined populations (cirrhotic and non-cirrhotic) were used.

Due to a lack of efficacy and safety data in GT4 patients, data from GT1 patients was used for SOF+PR 1-12, LDV/SOF 1-12 and DCV+SOF 1-12 treatment regimens, as the efficacy and safety of both treatment regimens is assumed to be equivalent. For DCV+PR 1-24, no trials report a treatment-experienced population; therefore, a conservative approach was taken by using data from treatment-naïve patients. Finally, the OMB+PAR/r+R 1-24 regimen has not been evaluated in patients with GT4 in a clinical trial. The marketing authorisation for this regimen is based on data for OMB+PAR/r 1-24 in genotype 1b patients, so the same data was used to inform the analysis of both SVR and safety outcomes. Finally, the only trial of SMV+PR 1-12, PR 13-48 in genotype 4 patients (RESTORE) was carried out in both

patients with and without cirrhosis, therefore this combined population was used for the comparisons.

4.10.9; 4.10.10; 4.10.11 Methods, outcomes, baseline characteristics, risk of bias

A brief summary of the characteristics of all included trials, as well as patient characteristics at baseline in relevant treatment arms, are presented in Appendix 9. The validity of individual trials was assessed using the Risk of Bias instrument endorsed by the Cochrane Collaboration. The results of these assessments are also presented in Appendix 6.

4.10.12 Methods of analysis and presentation of results

The large number of non-comparative trials included within this evidence base necessitated the use of a novel approach to NMA. Two techniques were implemented to measure treatment comparisons across trials:

- Naïve comparisons: for all interventions, pooled proportions were calculated. All pairs of interventions were then compared using basic statistical methods (e.g., 2x2 contingency tables and Normal test for difference), which assumes that treatments are independent.
- NMA with imputed control arms: for each non-comparative trial, an imputed PR control arm was created, estimated from the PR arms of comparative trials. A connected network of evidence was thus developed where the non-comparative trials connect through their imputed PR arms allowing NMA to be performed.

In order for imputed control arms to be utilised, this method assumes that trials are relatively similar within subgroups. As discussed in Section 4.10.8, the NMA were performed on highly restricted specific subgroups, therefore it is reasonable to assume that the similarity condition for NMA holds i.e. balance in the distribution of effect modifiers between studies comparing different interventions. In situations where there were no comparative trials for a particular subgroup, and consequently no data with which to create imputed controls, it was not possible to perform an NMA. For these subgroups, only naïve comparisons are presented. More details on both analytical approaches can be found below.

Naïve comparisons

All study arms pertaining to a given regimen were combined to obtain pooled proportions, where the numerator is the sum of events and the denominator is the sum of the number of patients. To allow the use of a Normal approximation for the data's underlying distribution, standard errors were calculated using a continuity correction if any studies had a pooled

proportion of 0 or 1, i.e., 0.5 was added to all cell frequencies of studies with a zero cell count. A Normal distribution assumption was then used to calculate 95% confidence intervals (CIs) and truncated at 0 and 1. Pooled proportions were compared between all regimens as relative risks ($proportion_A/proportion_B$). Again, if a pooled proportion was equal to 1, the 95% CI of the relative risk (RR) was adjusted using a treatment arm continuity correction, which adjusts zero cells relative to the number of patients in the two groups. This method does not account for any trial or patient characteristics, assumes that treatments are independent, and has no means of assessing within or between-trial variability. This is the least robust method of comparing treatments across trials.

Network meta-analysis

The evidence base for HCV treatment regimens includes non-comparative trials, particularly for the newer, all-DAA regimens, which poses a challenge when conducting comparative efficacy and safety analyses. Robust analysis techniques, such as NMA, typically require a means of controlling for between trial heterogeneity, which is the true variation in treatment effects caused by systematic differences in known and unknown study-design and patient related effect modifiers across studies. This can be accomplished by trial or patient characteristic adjustment and/or the presence of a connected network of evidence.

NMA is typically approached in a step-wise fashion. The first step is to conduct traditional pairwise meta-analysis for each direct comparison. Next, the feasibility of NMA is determined, which includes the assessment of the distribution of study and patient characteristics that may affect treatment effects across direct comparisons of the evidence network, and determining the existence of a connected network of evidence. Outlying trial characteristics are identified from plots of each characteristic across studies, within and between direct comparisons. Next, NMA is performed. Lastly, sensitivity analysis is conducted if there are trials with outlying characteristics that may potentially bias results. This can be checked and accounted for by conducting the NMA excluding these outlying trials from the evidence network or by adjustment using meta-regression.

The use of traditional NMA hinges on two conditions. The first is consistency of direct and indirect evidence within closed loops. The second is that the network must be connected. The second condition is not met in this evidence base for multiple comparators. For example, LDV/SOF and DCV+SOF have not been featured in any head-to-head trials, and only OMB+PAR/r+DAS ± R 1-12 of the 3D/2D regimens has been compared directly with another comparator (TVR).

In order to include non-comparative trials in the NMA, imputed control arms were implemented. This approach has been presented at the 2015 International Society for

Pharmacoecomics and Outcomes Research (ISPOR) conference in Milan[106], and has been used by the Canadian Agency for Drugs and Technologies in Health (CADTH) in their therapeutic review of treatment for HCV[107] as well as the World Health Organization (WHO) in the evidence synthesis used to inform their 2016 HCV treatment guidelines[108].

Historically PR has been the main control used in comparative trials, though one of the included OMB/PAR/r+DAS trials used TVR+PR. The PR control arms within included trials were therefore used as the basis for this imputation. For a given subgroup and outcome, the range of outcome response in the PR arms in comparative trials was ascertained. The pooled average value for SVR, discontinuation, and AEs rates were calculated and used to impute a PR arm for the non-comparative trials, which can be viewed as akin to mean imputation. Trials with PR arms that did not include a comparator of interest were included in circumstances either where it was not possible to create a network or where they allowed for additional direct comparisons within an existing network.

In creating the imputed control arms, the sample sizes in each non-comparative trial arm were reduced to avoid artificially increasing precision. For example, in a two arm trial in which the imputed arm is a third arm, the sample size from each observed arm are reduced by a third and the imputed arm is set to the same size as the reduced arms. The number of cases is reduced by the same factor so as to conserve the probability of the event. This adjustment ensures that estimation intervals do not become narrower based on the addition of data that were never observed.

The NMAs were performed in the Bayesian framework. Both fixed and random effects models were run, with results presented as relative risks (RRs). RRs were selected over odds ratios as they were expected to be more stable as well as being more readily interpretable.

4.10.13 Programming language

The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the OpenBUGS software package. A first series of iterations from the OpenBUGS sampler was discarded following 50,000 iterations ‘burn-in’, and the inferences were based on an additional 50,000 iterations using two chains. All analyses were performed using R version 3.2.2 (http://www.r-project.org/) and OpenBugs version 3.2.3 (OpenBUGS Project Management Group). Programming language has been provided in Appendix 7.

4.10.14; 4.10.15; 4.10.16 Results of analysis and results of statistical assessment of heterogeneity

Sustained Virologic Response

GT1a: Treatment naïve, without cirrhosis

For patients who are GT1a, TN, and NC, the pooled SVR for EBR/GZR 1-12 is 96.72% (95% CI 95.04, 98.40). Similar pooled SVRs were observed for the other IFN-free regimens. In the both the naïve comparisons and NMA, no statistically meaningful differences were observed between EBR/GZR 1-12 and the other all-DAA regimens.

Table 38. NMA SVR results for therapies for GT1a TN NC patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	481 (6)	96.72 (95.04, 98.40)	--	--
PR 1-48	649 (4)	49.96 (46.16, 53.77)	**1.90 (1.76, 2.06)**	**1.86 (1.70, 2.03)**
SMV+PR 1-12, PR 13-24 or PR 13-48	537 (3)	81.76 (78.50, 85.03)	**1.16 (1.11, 1.21)**	**1.20 (1.09, 1.42)**
SOF+PR 1-12	31 (2)	97.61 (90.34, 100.00)	1.01 (0.92, 1.11)	1.05 (0.95, 1.46)
LDV/SOF 1-8	171 (1)	92.98 (89.15, 96.81)	1.02 (0.97, 1.07)	1.01 (0.95, 1.16)
OMB+PAR/r+DAS+R 1-12	491 (3)	96.10 (94.39, 97.81)	0.99 (0.96, 1.02)	0.98 (0.93, 1.03)
DCV+SOF 1-12	60 (1)	96.67 (92.12, 100.00)	0.98 (0.93, 1.03)	0.98 (0.93, 1.13)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

GT1a: Treatment naïve, with cirrhosis

For patients with GT1a, who are TN and C, the pooled SVR for EBR/GZR 1-12 was 96.23% (95% CI 92.15, 100.00). The only regimen with a higher pooled SVR was LDV/SOF 1-12 (97.15% [95% CI 91.65, 100.00]). In the both the naïve comparisons and NMA, no statistically meaningful differences were observed between EBR/GZR 1-12 and the other all-DAA regimens.

Table 39. NMA SVR results for therapies for GT1 TN C patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	104 (5)	96.23 (92.15, 100.00)		
PR 1-48	32 (2)	34.00 (17.68, 50.31)	**2.77 (1.71, 4.48)**	**2.68 (2.00, 3.80)**
SMV+PR 1-12, PR 13-24 or PR 13-48	48 (2)	60.51 (46.72, 74.31)	**1.58 (1.25, 1.99)**	**1.50 (1.06, 3.90)**
SOF+PR 1-12	10 (1)	80.00 (55.21, 100.00)	1.19 (0.87, 1.63)	1.18 (0.96, 7.19)
LDV/SOF 1-12	59 (4)	97.15 (91.65, 100.00)	0.99 (0.92, 1.05)	1.00 (0.92, 1.11)
OMB+PAR/r+DAS+R 1-24	56 (1)	92.86 (86.11, 99.60)	1.03 (0.94, 1.12)	1.04 (0.94, 1.78)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

GT1a: Treatment experienced, without cirrhosis

For patients who are GT1a, TE, and NC, the pooled SVR for EBR/GZR 1-12 was 92.65% (95% CI 85.59, 99.72). LDV/SOF 1-12, OMB+PAR/r+DAS+RBV 1-12, and DCV+SOF 1-12 reported higher pooled SVR than EBR/GZR 1-12 (98.26% [95% CI 96.45, 100.00], 96.58% [95% CI 93.88, 99.28], and 100.00% [95% CI 29.10, 100.00], respectively). Of note, data for DCV+SOF 1-12 comprised one trial with 20 patients. In the naïve comparison, the difference between EBR/GZR 1-12 and DCV+SOF 1-12 was statistically significant (RR 0.92 [95% CI 0.86, 0.99]), but no statistically meaningful differences were observed in the NMA versus the other all-DAA regimens.

Table 40. NMA SVR results for therapies for GT1a TE NC patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	62 (4)	92.65 (85.59, 99.72)		--
PR 1-48	113 (1)	38.05 (29.10, 47.00)	**2.42 (1.89, 3.09)**	**2.28 (1.68, 2.95)**
SMV+PR 1-12, PR 13-24 or PR 13-48	211 (1)	80.09 (74.71, 85.48)	**1.15 (1.04, 1.27)**	1.13 (0.87, 2.55)
SOF+PR 1-12	69 (2)	79.93 (70.44, 89.42)	**1.15 (1.00, 1.33)**	1.12 (0.86, 2.17)
LDV/SOF 1-12	254 (4)	98.26 (96.45, 100.00)	0.96 (0.89, 1.03)	0.96 (0.76, 1.04)
OMB+PAR/r+DAS+R	192 (2)	96.58 (93.88,	0.95 (0.88, 1.03)	0.96 (0.76, 1.07)

1-12		99.28)		
DCV+SOF 1-12	20 (1)	100.00 (29.10, 100.00)	**0.92 (0.86, 0.99)**	0.97 (0.77, 1.37)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

GT1a: Treatment experienced, with cirrhosis

For patients who are GT1a, TE, and C, the pooled SVR for EBR/GZR 1-12 was 91.14% (95% CI 81.32, 100.00). Both the interferon-free regimens LDV/SOF 1-12 and OMB+PAR/r+DAS+RBV 1-24 reported higher pooled SVRs than EBR/GZR 1-12 (98.48% [95% CI 94.64, 100.00] and 95.38% [95% CI 90.28, 100.00], respectively). In the both the naïve comparisons and NMA, no statistically meaningful differences were observed between EBR/GZR 1-12 and the other all-DAA regimens.

Table 41. NMA SVR results for therapies for GT1a TE C patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	34 (3)	91.14 (81.32, 100.00)		
PR 1-48	19 (1)	26.32 (6.52, 46.12)	**3.46 (1.62, 7.41)**	**4.03 (2.23, 6.79)**
SMV+PR 1-12, PR 13-24 or PR 13-48	39 (1)	74.36 (60.65, 88.06)	1.23 (0.99, 1.52)	1.30 (0.79, 17.76)
SOF+PR 1-12	14 (1)	71.43 (47.76, 95.09)	1.28 (0.90, 1.81)	1.33 (0.77, 26.22)
LDV/SOF 1-12	77 (4)	98.48 (94.64, 100.00)	0.99 (0.87, 1.12)	0.99 (0.63, 1.22)
OMB+PAR/r+DAS +R 1-24	65 (1)	95.38 (90.28, 100.00)	0.96 (0.85, 1.08)	1.00 (0.66, 3.14)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

GT1b: Treatment naïve, without cirrhosis

For patients who are GT1b, TN, and NC, the pooled SVR for EBR/GZR 1-12 was 98.27% (95% CI 96.59, 99.94). The only regimens with a higher pooled SVR were OMB+PAR/r+DAS 1-12 (98.84% [95% CI 97.62, 100.00]) and DCV+SOF 1-12 (100.00 [95% CI 46.16, 100.00]). In the naïve comparison, the difference between EBR/GZR 1-12 and DCV+SOF 1-12 was statistically significant (RR 0.97 [95% CI 0.95, 0.99]), but no statistically meaningful differences were observed in the NMA versus the other all-DAA regimens.

Table 42. NMA SVR results for therapies for GT1b TN NC

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	272 (6)	98.27 (96.59, 99.94)		
PR 1-48	649 (4)	49.96 (46.16, 53.77)	**1.95 (1.80, 2.11)**	**1.92 (1.67, 2.25)**
SMV+PR 1-12, PR 13-24 or PR 13-48	537 (3)	81.76 (78.50, 85.03)	**1.19 (1.14, 1.24)**	**1.24 (1.11, 1.53)**
SOF+PR 1-12	64 (2)	96.76 (92.29, 100.00)	1.00 (0.95, 1.05)	1.00 (0.97, 1.09)
LDV/SOF 1-8	43 (1)	97.67 (93.17, 100.00)	0.99 (0.94, 1.05)	1.02 (0.97, 1.27)
OMB+PAR/r+DAS 1-12	292 (2)	98.84 (97.62, 100.00)	0.98 (0.96, 1.01)	0.99 (0.96, 1.02)
DCV+SOF 1-12	12 (1)	100.00 (46.16, 100.00)	**0.97 (0.95, 0.99)**	1.00 (0.97, 1.50)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response

GT1b: Treatment naïve, with cirrhosis

For patients who are GT1b, TN, and C, the pooled SVR for EBR/GZR 1-12 was 100.00% (95% CI 17.68, 100.00). The only regimen with a comparable pooled SVR was OMB+PAR/r+DAS+RBV 1-12 (100.00% [95% CI 96.83, 100.00]). In the both the naïve comparisons and NMA, no statistically meaningful differences were observed between EBR/GZR 1-12 and the other all-DAA regimens.

Table 43. NMA SVR results for therapies for GT1b TN C

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	78 (6)	100.00 (17.68, 100.00)		
PR 1-48	32 (2)	34.00 (17.68, 50.31)	**2.86 (1.79, 4.58)**	**2.89 (2.11, 4.25)**
SMV+PR 1-12, PR 13-24 or PR 13-48	48 (2)	60.51 (46.72, 74.31)	**1.65 (1.31, 2.07)**	**1.58 (1.06, 5.45)**
SOF+PR 1-12	12 (1)	91.67 (76.03, 100.00)	1.09 (0.92, 1.29)	1.09 (0.99, 4.37)
LDV/SOF 1-12	59 (4)	97.15 (91.65, 100.00)	1.03 (0.99, 1.09)	1.01 (0.96, 1.16)
OMB+PAR/r+DAS +R 1-12	22 (1)	100.00 (96.83, 100.00)	1.00 (0.95, 1.05)	1.01 (0.97, 1.62)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

GT1b: Treatment experienced, without cirrhosis

For patients who are GT1b, TE, and NC, the pooled SVR for EBR/GZR 1-12 was 99.12% (95% CI 95.12, 100.00). The only regimens with a higher pooled SVR were OMB+PAR/r+DAS 1-12 (100.00% [95% CI 29.10, 100.00]) and DCV+SOF 1-12 (100.00% [95% 95.12, 100.00]). In the both the naïve comparisons and NMA, no statistically meaningful differences were observed between EBR/GZR 1-12 and the other all-DAA regimens.

Table 44. NMA SVR results for therapies for GT1b, TE NC patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	63 (4)	99.12 (95.12, 100.00)		
PR 1-48	113 (1)	38.05 (29.10, 47.00)	**2.54 (2.00, 3.23)**	**2.58 (2.04, 3.32)**
SMV+PR 1-12, PR 13-24 or PR 13-48	211 (1)	80.09 (74.71, 85.48)	**1.21 (1.12, 1.31)**	1.22 (0.98, 5.25)
SOF+PR 1-12	36 (2)	84.68 (73.04, 96.32)	1.16 (1.00, 1.35)	1.16 (0.97, 3.37)
LDV/SOF 1-12	254 (4)	98.26 (96.45, 100.00)	1.01 (0.96, 1.06)	1.00 (0.89, 1.09)
OMB+PAR/r+DAS 1-12	91 (1)	100.00 (29.10, 100.00)	0.97 (0.93, 1.01)	0.99 (0.89, 1.21)
DCV+SOF 1-12	8 (1)	100.00 (95.12, 100.00)	0.97 (0.93, 1.01)	1.00 (0.90, 1.79)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

GT1b: Treatment experienced, with cirrhosis

For patients who are GT1b, TE, and C, the pooled SVR for EBR/GZR 1-12 was 100.00% (95% CI 6.52, 100.00). Similar pooled SVRs were observed for the other interferon-free regimens: 98.48% (95% CI 94.64, 100.00) for LDV/SOF 1-12 and 97.83% (95% CI 93.61, 100.00) for OMB+PAR/r+DAS+RBV 1-12. In the naïve comparison, the difference between EBR/GZR 1-12 and LDV/SOF 1-12 was statistically significant (RR 1.08 [95% CI 1.02, 1.16]), but no statistically meaningful differences were observed in the NMA versus the other all-DAA regimens.

Table 45. NMA SVR results for therapies for GT1b TN C patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	16 (3)	100.00 (6.52, 100.00)		
PR 1-48	19 (1)	26.32 (6.52, 46.12)	**3.53 (1.74, 7.13)**	**3.58 (2.10, 6.13)**
SMV+PR 1-12, PR 13-24 or PR 13-48	39 (1)	74.36 (60.65, 88.06)	**1.34 (1.12, 1.60)**	1.27 (0.84, 17.95)
SOF+PR 1-12	8 (1)	50.00 (15.35, 84.65)	**1.92 (1.00, 3.69)**	1.60 (0.93, 55.93)
LDV/SOF 1-12	77 (4)	98.48 (94.64, 100.00)	**1.08 (1.02, 1.16)**	1.00 (0.70, 1.20)
OMB+PAR/r+DAS +R 1-12	46 (1)	97.83 (93.61, 100.00)	1.02 (0.98, 1.07)	1.02 (0.75, 4.08)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

GT14: Treatment naïve, without cirrhosis

For patients who are GT4, TN, and NC, the pooled SVR for EBR/GZR 1-12 was 96.97% (95% CI 91.54, 100.00). The only regimen with a higher pooled SVR was OMB+PAR/r+RBV 1-12 (100.00% [95% CI 23.93, 100.00]). In the naïve comparison, the difference between EBR/GZR 1-12 and OMB+PAR/r+RBV 1-12 was statistically significant (RR 0.93 [95% CI 0.86, 1.00]), but no statistically meaningful differences were observed in the NMA versus the other all-DAA regimens.

Table 46. NMA SVR results for therapies for GT4 TN NC patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	54 (4)	96.97 (91.54, 100.00)		
PR 1-48	38 (1)	39.47 (23.93, 55.01)	**2.35 (1.57, 3.50)**	**2.36 (1.57, 3.65)**
SMV+PR 1-12, PR 13-24 or PR 13-48	32 (1)	84.38 (71.79, 96.96)	1.10 (0.93, 1.30)	1.09 (0.84, 29.18)
OMB+PAR/r+R 1-12	42 (1)	100.00 (23.93, 100.00)	**0.93 (0.86, 1.00)**	1.00 (0.79, 4.62)
DCV+PR 1-24 or DCV+PR 1-24, PR 25-48	69 (1)	71.01 (60.31, 81.72)	**1.30 (1.10, 1.54)**	1.35 (0.90, 59.42)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

GT4: Treatment naïve, with cirrhosis

For patients who are GT4, TN, and C, the pooled SVR for EBR/GZR 1-12 was 100.00% (95% CI 0.00, 100.00). Similar pooled SVRs were observed for LDV/SOF 1-12 (97.15%

[95% CI 91.65, 100.00]) and OMB+PAR/r+RBV 1-24 (97.87% [95% CI 93.75, 100.00]). In the both the naïve comparisons and NMA, no statistically meaningful differences were observed between EBR/GZR 1-12 and the other all-DAA regimens.

Table 47. NMA SVR results for therapies for GT 4 TN C patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	6 (2)	100.00 (0.00, 100.00)		
PR 1-48	4 (1)	25.00 (0.00, 67.43)	3.14 (0.80, 12.34)	**5.26 (2.11, 9.85)**
SMV+PR 1-12, PR 13-24 or PR 13-48	3 (1)	66.67 (13.32, 100.00)	1.43 (0.71, 2.88)	1.23 (0.55, 82.71)
SOF+PR 1-12	74 (3)	83.77 (75.45, 92.09)	**1.21 (1.09, 1.34)**	1.11 (0.50, 2.17)
LDV/SOF 1-12	59 (4)	97.15 (91.65, 100.00)	1.03 (0.99, 1.08)	1.00 (0.44, 1.21)
OMB+PAR/r+R 1-24	47 (1)	97.87 (93.75, 100.00)	1.02 (0.98, 1.06)	1.02 (0.49, 3.23)
DCV+PR 1-24 or DCV+PR 1-24, PR 25-48	9 (1)	77.78 (50.62, 100.00)	1.26 (0.91, 1.75)	1.25 (0.57, 18.75)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

GT4: Treatment experienced, without cirrhosis

For patients who are GT4, TE, and NC, the pooled SVR for EBR/GZR 1-12 was 100.00% (95% CI 29.10, 100.00). Two regimens reported the same pooled SVR: OMB+PAR/r+RBV 1-12 (100.00% [95% CI 74.30, 100.00]) and DCV+SOF 1-12 (100.00% [95% CI 49.42, 100.00]). In the naïve comparison, the difference between EBR/GZR 1-12 and LDV/SOF 1-12 was statistically significant (RR 1.04 [95% CI 1.02, 1.07]), but no statistically meaningful differences were observed in the NMA versus the other all-DAA regimens.

Table 48. NMA SVR results for therapies for GT4 TE NC patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	5 (2)	100.00 (29.10, 100.00)		
PR 1-48	113 (1)	38.05 (29.10, 47.00)	**2.59 (2.06, 3.27)**	2.59 (0.91, 3.94)
SMV+PR 1-12, PR 13-24 or PR 13-48	44 (1)	63.64 (49.42, 77.85)	**1.55 (1.25, 1.93)**	1.43 (0.55, 26.21)
LDV/SOF 1-12	254 (4)	98.26 (96.45, 100.00)	**1.04 (1.02, 1.07)**	1.00 (0.38, 1.14)
OMB+PAR/r+R 1-12	49 (1)	100.00 (74.30, 100.00)	1.00 (0.88, 1.13)	1.00 (0.39, 1.87)
DCV+PR 1-24 or DCV+PR 1-24, PR	69 (1)	71.01 (60.31, 81.72)	**1.40 (1.21, 1.62)**	1.34 (0.55, 22.38)

25-48				
DCV+SOF 1-12	28 (1)	100.00 (49.42, 100.00)	1.00 (0.85, 1.18)	1.00 (0.40, 2.11)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

GT4: Treatment experienced, with cirrhosis

For patients who are GT4, TE, and C, the pooled SVR for EBR/GZR 1-12 was 66.67% (95% CI 28.95, 100.00). The highest pooled SVRs were observed for LDV/SOF 1-12 (98.48% [95% CI 94.64, 100.00]) and OMB+PAR/r+RBV 1-24 (96.15% [95% CI 90.93, 100.00]). In the both the naïve comparisons and NMA, no statistically meaningful differences were observed between EBR/GZR 1-12 and the other all-DAA regimens.

Table 49. NMA SVR results for therapies for GT4 TE C patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	6 (1)	66.67 (28.95, 100.00)		
PR 1-48	19 (1)	26.32 (6.52, 46.12)	2.53 (0.99, 6.49)	2.47 (0.06, 5.67)
SMV+PR 1-12, PR 13-24 or PR 13-48	28 (1)	46.43 (27.96, 64.90)	1.44 (0.72, 2.87)	1.45 (0.04, 30.13)
SOF+PR 1-12	22 (2)	64.61 (45.07, 84.15)	1.05 (0.55, 2.00)	0.96 (0.03, 6.40)
LDV/SOF 1-12	77 (4)	98.48 (94.64, 100.00)	0.72 (0.41, 1.28)	0.65 (0.02, 1.09)
OMB+PAR/r+R 1-24	52 (1)	96.15 (90.93, 100.00)	0.69 (0.39, 1.22)	0.68 (0.02, 2.03)
DCV+PR 1-24 or DCV+PR 1-24, PR 25-48	9 (1)	77.78 (50.62, 100.00)	0.86 (0.44, 1.67)	0.70 (0.02, 3.10)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviation:** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response

Full details of all the efficacy results can be found in Appendix 10.

Safety Outcomes

GT1: Without cirrhosis

EBR/GZR had a better safety profile across all outcomes compared to regimens containing Peg-IFN and/or RBV (PR 1-48, SMV+PR 1-12, PR 13-24, SOF+PR, and OMB+PAR/r+DAS+R 1-12). In the NMA, statistically meaningful differences were observed for OAE (all PR containing regimens), DAE (PR 1-48, SMV+PR 1-12, PR 13-24), aneamia (all Peg IFN and/or RBV containing regimens), nausea (PR 1-48, SMV+PR 1-12, PR 13-24, and OMB/PAR/r+DAS+R 1-12), neutropenia (all PR containing regimens), pruritus (all Peg

IFN and/or RBV containing regimens), and rash (all Peg IFN and/or RBV containing regimens). For the all-DAA regimens, the only statistically meaningful differences were between EBR/GZR and OMB/PAR/r+DAS 1-12, with RRs of 0.01 (95% CrI 0.00, 0.03) for neutropenia and 0.39 (95% CrI 0.18, 0.85) for pruritus.

GT1: With cirrhosis

A similar pattern to the one seen in patients without cirrhosis was observed for patients with cirrhosis, with outcomes for EBR/GZR being superior to the regimens named in the previous section plus OMB/PAR/r+DAS+R 1-24. In the NMA, statistically meaningful differences were observed for OAE (all PR containing regimens), DAE (PR 1-48, SOF+PR 1-12, PR), aneamia (all Peg IFN and/or RBV containing regimens), nausea (all PR containing regimens), neutropenia (all Peg IFN and/or RBV containing regimens except SOF+PR 1-12), pruritus (PR 1-48, SMV+PR 1-12, PR 13-24), and rash (all Peg IFN and/or RBV containing regimens except SOF+PR 1-12). No statistically meaningful differences with LDV/SOF 1-12, the only other all-DAA regimen, were observed.

GT4: Without cirrhosis

Data for GT4 was much more limited than for GT1, with no NMA possible for OAE, nausea, and rash. For the outcomes (DAE, aneamia, neutropenia and pruritus) where an NMA was run, statistically meaningful differences were observed between EBR/GZR and PR 1-48 in all four. The only other statistically meaningful difference was between rates of pruritus with EBR/GZR and DCV+PR (RR 0.01 [95% CrI 0.00, 0.18]).

GT4: With cirrhosis

No NMA were possible for OAE, nausea, and rash. The only statistical meaningful difference that was observed in the NMAs of the other four outcomes was between rates of pruritus with EBR/GZR and PR 1-48 (RR 0.03 [95% CrI 0.00, 0.95]).

Full details of all the safety results can be found in Appendix 10.

Summary of results

The NMA revealed no significant differences between SVR with EBR/GZR and the other all-DAA regimens (LDV/SOF, OMB+PAR/r ± DAS ± RBV, and DCV+SOF) in any of the subgroups that were investigated. Furthermore, with the exception of patients who are GT4, TE, and without cirrhosis, most of the RRs were close to 1 (ranging from 0.96 to 1.04). Of note, the NMA results show large CrI for SOF+PR and SMV +PR in cirrhotic patients; this is most likely due to the small number of patients assessed. Compared to the point estimates of the naïve comparisons, the NMA results were generally closer to 1. However, the results

of both analyses were broadly consistent, especially for the all-DAA regimens. In the safety analysis, EBR/GZR generally had lower rates of AE than regimens containing Peg IFN and/or RBV in patients with GT1, regardless of cirrhosis status. For GT4, fewer meaningful differences were observed.

4.10.17 Justification for the choice of random or fixed effects model

For both fixed and random effects models, the goodness-of-fit of model predictions to the observed data was measured by calculating the posterior mean residual deviance, and subsequently the deviance information criterion (DIC) was obtained which provides a measure of the trade-off between model fit and parsimony (the fixed effect model being the most parsimonious). The model with the better trade-off between fit and parsimony has a lower DIC. A difference in DIC of about 3 points can be considered meaningful. Since model fit is not a proxy for the plausibility of model assumptions, a lower DIC was not a sufficient reason alone to select fixed or random effects models. As a result, the random effects model was selected, despite fixed effects having the smaller DIC in most subgroups (ranging from 1.7 to 0.6 points lower), as it provided both a more realistic set of assumptions as well as more conservative estimates of the differences between treatments.

4.10.18; 4.10.19 Relevance of trials and heterogeneity between results of pairwise comparisons

Baseline characteristics were generally well balanced across trials, with the exception of Rodriguez-Torres et al., 2015[79] (Latino/Hispanic population), Lim et al., 2015[88] (Asian population), Mizokami et al., 2015[89] (Asian population), SYNERGY (Black/African American population), C-SURFER (CKD patients) [14], C-EDGE TN[59] (Asian population in GT1b and 4, TN, with or without cirrhosis), C-EDGE CO-STAR[63] (Black/African American in GT1b, TN, with cirrhosis), C-EDGE TE[60] (Asian population in GT1b, TE, with cirrhosis). Sensitivity analyses with these trials excluded were consistent with the overall results.

There was a high degree of consistency between the direct evidence included with the analysis and the results of the NMA. Plots of direct versus indirect estimates are presented in Appendix 11.

4.11 Non-randomised and non-controlled evidence

4.11.1 Non-randomised evidence

C-EDGE COINFECTION was identified via electronic database searches as described in section 4.1. This trial enrolled 218 patients with HCV/HIV co-infection, all of which received EBR (50mg)/GZR (100mg) for 12 weeks as single tablet FDC[74].

Table 50. Included non-randomised clinical trials

C-EDGE CO-INFECTION[74] NCT02105662 PN061	
Objective	Primary objective • Evaluate the efficacy of EBR/GZR by the proportion of patients achieving SVR12 defined as HCV RNA <LLOQ (TDu or TND) • Evaluate the safety and tolerability EBR/GZR
Population	• TN; GT1a, 1b, and 4; cirrhotic and non-cirrhotic patients
Intervention	Intervention • EBR (50mg)/GZR (100mg) 12 weeks Comparator • NA
Justification for inclusion	• Study reports patients enrolled from UK centres (NICE reference case). However, it is not expected that geographical location would impact on the treatment duration or treatment outcome of patients with confirmed GT1a, 1b, and or 4 infections that satisfy the inclusion/exclusion criteria of the included RCTSs. • Study reports a HIV co-infected population. As described in section 3.6, EASL guidelines do not differentiate treatment outcomes or treatment regimen in those patients with HCV HIV co-infection, and therefore are relevant to this decision problem. • Study reports GT4 infected patients. Due to a paucity of GT4 data the decision was made to include these patients so as to provide a robust effect estimate.

Abbreviations. GT, genotype; EBR/GZR, grazoprevir/elbasvir; HCV, hepatitis C virus; IU, international units; LLOQ, lower limit of quantification; RNA, ribonucleic acid; SVR, sustained virologic response; TDu, target detected unquantifiable; TN, treatment naïve; TND, target not detected;

4.11.2 Trials excluded from further discussion

Not applicable.

4.11.3 Summary of Non-RCT Study methodology

Table 51. C-EDGE CO-INFECTION summary of methodology

Trial Name, NCT number	C-EDGE CO-INFECTION[74] NCT02105662
Location	This study was conducted at 37 study centres in the following countries: USA, Australia, Canada, Denmark, France, Germany, Israel, Spain, and the UK.
Trial design	• Phase III open-label clinical trial • Designed to enrol ~200 patients, all to be HIV co-infected and TN to all HCV therapy including DAAs. Enrolment was managed to ensure that ~20% of patients had compensated cirrhosis. • All patients to receive 12 weeks EBR/GZR, with 24 weeks follow-up, once dosing was complete.
Eligibility criteria for participants	Key inclusion criteria, include but was not limited to: • Aged ≥18 year and provide written consent • HCV RNA (≥ 10,000 IU/mL in peripheral blood) at the time of screening

Trial Name, NCT number	C-EDGE CO-INFECTION[74] NCT02105662
	• have documented chronic HCV GT1, GT4, GT6 (with no evidence of non typeable or mixed genotype) infection: • have liver disease staging assessment as follows: • A liver biopsy performed prior to Day 1 of this study showing cirrhosis (F4) • Fibroscan performed within 12 calendar months of Day 1 of this study showing cirrhosis with result >12.5 kPa • A FibroSure® (Fibrotest®) performed during Screening with a score of >0.75 and an aspartate aminotransferase (AST): platelet ratio index (APRI) of >2 . APRI formula: AST÷lab upper limit of normal (ULN) for AST x 100÷platelet count÷100 (APRI calculation to be provided by the central laboratory.) • be HIV-1 infected, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA viral load • currently, are naïve to treatment with any antiretroviral therapy or be on HIV Antiretroviral Therapy (ART) for at least 8 weeks prior to study entry using a dual NRTI backbone of tenofovir or abacavir and either emtricitabine or lamivudine PLUS Raltegravir Dose modifications or changes in drugs during the 4 weeks prior to study entry are not permitted. Patients not on ART should have no plans to initiate therapy through at least Follow-up Week 4 of this study. Patients on ART should plan to remain on the same therapy through at least Follow-up Week 4 of this study. • CD4+ T-cell count > 200 cells/mm3 at screening (for patients currently on stable ART); CD4+ T-cell count >500 cells/mm3 at screening (for patients who are naïve to treatment with ART). • Have documented undetectable plasma HIV-1 RNA at screening and at least 8 weeks prior to screening. For patients not on ART, HIV RNA must be <50,000 copies/mL. Major exclusion criteria included but were not limited to: • is co-infected with hepatitis B virus • has evidence of decompensated liver disease • has cirrhosis and liver imaging within 6 months of Day 1 showing evidence of hepatocellular carcinoma (HCC) or is under evaluation for HCC • has a clinically-relevant drug or alcohol abuse within 12 months of screening • For patients with HIV, history of opportunistic infection in the preceding 6 months prior to screening Full details relating to inclusion and exclusion criteria are reported in section 9.3.1 and 9.3.2 of the C-EDGE COINFECTION CSR.
Settings and locations where the data were collected	Patients were treated in the hospital setting at 37 study centres.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were	EBR/GZR 12 weeks administered once daily

Trial Name, NCT number	C-EDGE CO-INFECTION[74] NCT02105662
administered) **Intervention(s) (n=) and comparator(s) (n=)** **Permitted and disallowed concomitant medication**	This study was non-comparative The list of prohibited medications includes but was not limited to: known hepatotoxic drugs, herbal supplements, CYP3A/P-gp inducers, OATP inhibitors, HIV medications listed, HMG-CoA etc. please see 9.4.6 of the C-EDGE COINFECTION CSR.
Primary outcomes (including scoring methods and timings of assessments)	• To evaluate the efficacy of EBR in combination with GZR as assessed by the proportion of patients achieving SVR12, defined as HCV RNA <LLOQ (either TD[u] or TND) 12 weeks after the end of all study therapy. • Primary hypothesis states that EBR/GZR will be superior to a historic control SVR12 rate of 70%. • HCV RNA was to be measured at Day 1, every two weeks through to treatment week 12, and then at follow-up weeks 4, 8, 12 and 24. • To evaluate the safety and tolerability of EBR in combination with GZR • Review of AE and SAE occurred at screening, days 1 and 7, every two weeks through to treatment week 12, and then at follow-up weeks 4, 8, 12 and 24.
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	Secondary objectives • Evaluate the efficacy of EBR in combination with GZR as assessed by the proportion of patients achieving SVR24, defined as HCV RNA <LLOQ (either TD(u) or TND) 24 weeks after the end of all study therapy. ○ This endpoint is not included in the current CSR as time point has not yet been reached by all patients. This will be summarised in a future report, date to be confirmed. Other objectives • Evaluate the efficacy of EBR/GZR by the proportion of patients achieving undetectable (TND) HCV RNA and HCV RNA <LLOQ at Weeks 2, 4, 12, and Follow-Up Week 4 (SVR4). • Describe patient-reported outcomes related to HRQoL, fatigue, and work productivity/activity impairment before, during, and after treatment with EBR/EBR. (not currently available in CSR) • Evaluate the emergence of viral resistance associated variants (RAVs) to EBR/GZR • Evaluate the pharmacokinetics (PK) of EBR/GZR (not available in current CSR) • Explore the relationship between genetic variation and patient response to the treatment • Evaluate the proportion of patients who develop HIV-1 virologic failure confirmed on two consecutive tests at least 2 weeks apart, in patients compliant with their HIV ARV therapies during protocol therapy. • Evaluate the effect of the study regimen on CD4+ T-cell counts *The secondary and explorative objectives described above have not been considered within this submission and are reported for completeness only.*
Pre-planned subgroups	Not Applicable
Additional information	To address the decision problem, data from this study were re-analysed in a post-hoc analysis to consider the following patients populations only:

Trial Name, NCT number	C-EDGE CO-INFECTION[74] NCT02105662
	• GT1a TN C • GT1a TN NC • GT1b TN C • GT1b TN NC • GT4 TN C • GT4 TN NC Therefore, two patients one with GT6 and one with GT1-other infection were excluded from these analyses.

Abbreviations. AE, adverse event; ART, anti-retro viral therapy; CSR, clinical study report; DAA, direct acting antiviral; GT, genotype; EBR/GZR, grazoprevir/elbasvir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LLoQ, lower limit of quantification; PK, pharmacokinetic; RAV, resistance associated variants; SAE, serious adverse event; SVR, sustained virologic response; TND, target not detected

4.11.4 Statistical analysis of the non-randomised evidence

Table 52. C-EDGE CO-INFECTION summary of statistical methodology

Trial number (acronym)	C-EDGE CO-INFECTION[74] NCT02105662
Primary analysis population	Primary efficacy endpoint • FAS population, this includes all randomised patients who received at least one dose of study medication Primary safety endpoint • APaT, this included all patients who received at least one dose of study treatment. • *In the context of this study the FAS and the APaT are identical by definition*
Sample size	• Estimated that 200 patients needed, and assuming a true response rate of 85%, the study had 90% power to demonstrate that the SVR12 rate is superior to a historical reference rate of 70% at an overall one-sided 2.5% alpha-level. • Using the planned ~200 patients, if a specific AE is not observed among the 200 patients in the study, the probability is 97.5% that the underlying percentage of patients with that AE is <1.83%.
Statistical methods	Primary efficacy endpoint • Wald test was planned to be conducted at the time the protocol was written. However, only a small number of patients failed to achieve SVR12. As a result, the asymptotic method might produce unreliable inferences. Instead, the two-sided one-sample exact test was used to test the null hypothesis, and the Clopper-Pearson method was used to construct the 95% confidence intervals for the SVR12 rate. Primary safety endpoint • The Clopper-Pearson method was used to construct the 95% confidence intervals for the safety analysis
Missing data	Primary efficacy endpoint • Missing = Failure Primary efficacy endpoint • DAO: that is any missing values were excluded from the analysis.

Abbreviations. APaT, all patients as treated; DAO, data as observed; FAS, full analysis set; SVR, sustained virological response

4.11.5 Participant flow in non-randomised studies

Table 53 C-EDGE COINFECTION patient baseline characteristics

Characteristic	C-EDGE COINFECTION[74] EBR/GZR, 12 weeks N=218
Age,	
Mean (SD)	48.7 (8.9)
Median (range)	49 (21-71)
Gender, n (%)	
Male	183 (83.9)
Female	35 (16.1)
Race, n (%)	
White	167 (76.6)
African American	38 (17.4)
Asian	6 (2.8)
Other…	7 (3.2)
HCV genotype, n (%)	
GT1 overall	NA
GT1a	144 (66.1)
GT1b	44 (20.2)
GT1 other	1 (0.5)
GT4	28 (12.8)
GT5	NA
GT6	NA
IL28B CC genotype, n (%)	77 (35.3)
IL28B non-CC genotype, n (%)	141 (64.7)
HCV baseline severity, n (%)	
≤ 800 000 IU/mL	NR
> 800 000 IU/mL	NR
Baseline HCV (log10 IU/ml),	
Mean (SD)	6.31 (6.37)
Fibrosis status, n (%)	
F0-F2	160 (73.4)
F3	23 (10.6)
F4	35 (16.1)
Special populations, n (%)	
HIV positive	218 (100)
Treatment history, n (%)	
Naïve	218 (100)

Abbreviation: GT, genotype; EBR/GZR, grazoprevir/elbasvir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NA, not applicable; NR, not reported; SD, standard deviation

Table 54 C-EDGE CO-INFECTION patient disposition

	C-EDGE CO-INFECTION[74] NCT02105662
Patient disposition	• 261 patients were screened for inclusion, of which 43 were not enrolled in the study. • A total of 218 patients were included and received study medication • 217 patients completed study medication, as 1 patient discontinued due to protocol deviation • 216 patients completed protocol specified study visits during treatment and through 12 weeks of follow-up; two patients were lost to follow-up • No patient discontinued related to AE • No patient discontinued due to a lack of efficacy

Abbreviation: AE, adverse event

4.11.6 -4.11.9 Quality assessment of the relevant non-randomised and non-controlled clinical trials

Due to the availability of the manufacturer CSR, C-EDGE CO-INFECTION was also assessed using the Cochrane risk of bias assessment tool (RCTs). This decision was based on the inclusion of multiple single arm studies into the NMA and allowed for a conservative, but consistent, review of the evidence base. This is presented below.

Table 55. C-EDGE CO-INFECTION[74] quality assessment

Type of bias	Review authors judgment	Support for judgment
Selection bias (Random sequence generation)	High risk	Non-randomized study
Selection bias (Allocation concealment)	High risk	Non-randomized study
Performance bias	High risk	Open-label
Detection bias	High risk	Open-label
Attrition bias	Low risk	The full analysis set, consisting of all patients who received at least one dose of study treatment, was used as the primary population for efficacy analyses.
Reporting bias	Low risk	Pre-specified outcomes are reported
Other bias	Unclear risk	Funding by Merck Sharp & Dohme Corp.

4.11.10-4.11.12 Clinical effectiveness result of the relevant non-randomised and non-controlled evidence

C-EDGE COINFECTION[74]

The primary endpoint, SVR12, reported in the FAS population was 95% (95% CI; 91.2-97.5) p<0.001 irrespective of GT or cirrhosis stage (Table 56). The SVR12 rate observed supports the hypothesis, that the true SVR12 rate is >70% as per the historical control. The CSR also reported the breakdown of SVR 12 for GT1a (n=136/144, 94.4%), GT1b (n=42/44, 95.5%),

and GT4 (n=27/28, 96.4%). However, these results are not split according to cirrhosis stage and were not pre-specified in the primary objective.

Table 56 Summary of clinical effectiveness results for non-randomised studies

Treatment outcome	Treatment regimen: EBR/GZR 12 weeks		
	n/N	%	95% CI†
Primary endpoint			
SVR 12, FAS GT1a, GT1b, GT1other, GT4, and GT6 overall	207/218	95	91.2-97.5. p<0.001*

Abbreviations. FAS, full analysis set, EBR/GZR, grazoprevir/elbasvir; GT, genotype
†Based on Clopper-Pearson method
*Based on a one sided exact test for a binomial proportion. A one sided p-value <0.025 supports that the true SVR12 is >70%

4.12 Adverse reactions

4.12.2 Adverse reactions reported in RCTs listed in section 4.2

C-EDGE TN Study, NCT02105467[59]

The authors of the CSR reported that EBR/GZR was generally well tolerated with a similar safety profile in both cirrhotic and non-cirrhotic patients. Overall, AEs occurred in 67.4% (n=213/316) and 68.6% (n=72/105) at a frequency of ≥5% in patients in the immediate and placebo group, respectively. Drug related AEs, as determined by the investigator, occurred in 36.1% (n=114/316) and 39% (n=41/105) of patients in the active and placebo group, respectively; with a difference of -2.9% (95% CI, -13.7 to 7.5). The most commonly reported AEs were headache (16.5%), fatigue (15.5%), and nausea (8.9%); this was comparable in both the immediate and placebo treatment group. Serious AEs during treatment and within the first 14 follow-up days were reported in 2.8% (n=9/316) and 2.9% (n=3/105) of patients in the active and placebo groups, respectively; none of which were considered to be study drug related. Two deaths in the immediate treatment group were observed, but not considered study drug related. In total four patients discontinued therapy. Three of the four patients were randomised to the immediate treatment arm and discontinued treatment due to elevated transaminase to >5x ULN (n=2), and palpitations/anxiety (n=1). A single patient randomised to the placebo group discontinued related to a rash on day two of therapy; see Appendix 5 for a tabulated summary of AEs.

C-EDGE TE Study NCT02105701[60]

The authors of the CSR reported that EBR/GZR was generally well tolerated. The most commonly reported AE's across the trial were fatigue (23.1%), headache (19.8%), and nausea (11.0%) occurring at a similar frequency across treatment arms, and the majority of AEs were reported as either mild or moderate in severity. Not presented, but of note is that

regimens containing RBV were more poorly tolerated than non-RBV regimens. Serious AEs during treatment and within the first 14 follow-up days were reported in 3.8% (n=4/105) of patients, none of which were considered study drug related. No patient died during the study, but one patient died after the 14 day follow-up period due to cancer. One patient discontinued study therapy related to severe ascites; however, this was not considered to be study drug related.

In those patients with HCV/HIV co-infection there was no significant impact on CD3+/CD4+ cell counts, and no patient reported HIV-1 virological failure. The safety profile of HCV/HIV co-infected patients was similar to that in HCV mono-infected patients.

C-SCAPE Study NCT01932762[62]

The administration of EBR/GZR was generally well tolerated. Overall the most common AEs occurring at a frequency of >10% in the treatment arm of interest were: headache (26.3%), asthenia (21.1%), fatigue (15.8%), diarrhoea (15.8%), and insomnia (10.5%) (This is summarised in Appendix 5). The authors commented that the large number of events observed is most likely due to the small sample size (n=19). Of note, no patient reported a SAE or study drug related SAE. A single patient reported increased alanine- and aspartate-aminotransferase and discontinued study therapy, this AE was resolved.

C-EDGE CO-STAR Study NCT02105688[63]

The administration of EBR/GZR in patients in receipt of OST was generally well-tolerated, and the incidence of AE was generally similar between the immediate and deferred (placebo) treatment arms. The most commonly reported AEs, reported in more than 10% of patients, with similar frequency across treatment arms were; fatigue (15.9%), headache (12.4%), and nausea (10.9%). Overall, one or more AEs were reported in 82.6% (n=166/201) and 83% (n=83/100) of patients in the immediate or deferred treatment groups, respectively. The authors of the CSR comment that the AEs reported in C-CO-STAR are similar to those reported for other EBR/GZR trials, indicating that the concomitant use of OST as well as other illicit drug use did not affect the overall safety profile of the regimen.

Drug related AEs were reported in 41.3% (n=83/201) and 34% (n=34/100) of patients in the active and deferred (placebo) group during initial blinded therapy, respectively. Serious AEs were reported in 3.5% (n=7/201) and 4.0% (n=4/100) patients in the immediate and deferred treatment groups, respectively. Of note, a single patient in the immediate treatment arm reported a serious drug-related AE; this was reported as “worsening auditory hallucinations”. However, this patient achieved SVR12. One patient in the deferred (placebo) group experienced a serious drug-related AE, discontinued medication, and died related to acute

respiratory distress syndrome; this was not considered to be related to study drug. Two patients (one patient in each treatment arm during blinded therapy) discontinued study medication as a result of AEs. A summary of safety events is reported in Appendix 5.

C-SURFER Study NCT02092350[14]

The authors commented that the safety profile of EBR/GZR was comparable with placebo. The frequency of AEs was comparable between the immediate and deferred treatment groups at 75.7% and 84.1%, respectively. Most AEs were considered to be mild or moderate, irrespective of treatment group. The most common AEs (≥10% frequency) were headache (17.1%), nausea (15.3%), and fatigue (9.9%); these were comparable in the two groups (summarised in Appendix 5). A total of 16 (14%) patients in the immediate treatment group and 19 (17%) patients in the deferred treatment group reported a serious AE during treatment or within 14 days after the end of treatment. Two cases of congestive heart failure occurred in the immediate treatment group within 14 days of the end of treatment; one of these, judged by the investigator to be drug-related, was reported 6 weeks after study treatment ended. The authors commented that the SAE reported were consistent with the underlying co-morbidities and complications within this patient population.

There were four deaths, none considered related to study drug, during the initial treatment period plus 14 days. One patient in the immediate treatment group died from cardiac arrest, and three patients in the deferred treatment group died from aortic aneurysm, pneumonia, and an unknown cause of death. There were no discontinuations related to AEs in the immediate treatment group versus five patients in the deferred treatment group.

C-WORTHY Study NCT01717326[61]

The authors reported that EBR/GZR was generally well tolerated. The safety profile of EBR/GZR was similar across treatment arms (A2, B3, B5, B9, and B13) which included; TN, NC mono-infected patients, TN, NC HCV/HIV co-infection, TN C patients, and prior null responders to PR who were either C or NC.

Overall, the most common AEs in HCV GT1 infected patients were fatigue, headache, and nausea each of which were reported in more than 10% of all patients. One or more AE was observed in each of the treatment arms; A3 91.7% (n=11/12), B3 87.1% (n=27/31), B5 65.5% (n=19/29), B9 78.8% (n=26/33), and B13 53.3% (n=16/30). The number of serious AEs across the five treatment arms was low, range 0% (Arm A3, B3) to 6.9% (Arm B5, n=2/29). No patient discontinued the study related to an AE or SAE, study drug related or not. No patient died in the treatment arms of interest.

C-EDGE H2H Study NCT02358044[64]

The authors of the CSR reported that the safety profile for "tier 1" events for EBR/GZR compared with SOF+PR was statistically significantly better (the authors reporter superiority for EBR/GZR) with a between difference of -27% (95% CI -35.5 to -19.6) p<0.001 (see Appendix 5). Tier 1 events included but were not limited to: any serious drug related event including, any AE, or any drug related AE leading to permanent discontinuation of all study drugs.

The proportion of patients experiences an AE or drug related AE in the SOF+PR group was higher compared with EBR/GZR. In addition, only headache was reported at a frequency of >10% in patients randomised to EBR/GZR compared with patients in the SOF+PR arm who reported a events with a frequency of >10% for: pyrexia, headache, fatigue, asthenia, influenza-like illness, chills, myalgia, decreased appetite, aneamia, nausea, and cough. Similarly, the frequency of SAEs and drug related SAEs was higher in the SOF+PR arm vs. EBR/GZR. Overall the authors concluded that EBR/GZR once daily was generally well tolerated with a superior safety profile compared with SOF+PR.

4.12.3 Studies that report additional adverse reactions to those reported in section 4.2

MSD is not aware of any studies designed specifically to report safety. All relevant studies reporting EBR/GZR that also report safety were identified via electronic searching or provided through internal availability as described in section 4.1.

4.12.4 Brief overview of the safety of the technology in relation to the decision problem

Clinical data demonstrate that EBR/GZR has a favourable safety and tolerability profile when compared with placebo[14, 59, 63] or active control (SOF+PR)[64] for the treatment of patients with HCV GT1 and GT4 infections, irrespective of cirrhosis stage or treatment experience. EBR/GZR has been studied in a diverse patient population, including: CKD (stage 4-5), HIV and HCV co-infection, OST (and illicit drug use); and prior treatment failures (failed PR). Across these populations, the most commonly reported AEs included fatigue, headache, nausea, and in some cases diarrohea, dizziness, and cough. Across all studies discontinuation rates related to drug related AE or SAE were rare. Similarly, the rates of haematological abnormalities were also low, with a trend of increased aneamia associated with the use of RBV[60, 61, 64].

EBR/GZR represents an IFN-free treatment option for both patients and the NHS. In clinical practice this could potentially reduce resource use associated with the treatment of AE for regimens containing PR and could facilitate a higher throughput of patients. A favourable

safety profile for patients could mean improved patient experience with a reduced likelihood of discontinuation, related to AEs, leading to a greater likelihood of achieving SVR, which in turn could prevent the onward transmission of HCV.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

Key efficacy data relating to the treatment of HCV GT1a, GT1b, and GT4 infections split according to treatment experience and cirrhotic or non-cirrhotic patients has been reported in section 4.10. As previously described, post-hoc analysis has been used to inform this submission.

The evidence demonstrates that very high cure rates (SVR12) are achieved across GT1a (91-97%), GT1b (98-100%), and GT4 (67-100%) irrespective of cirrhosis state or treatment experience when treated with EBR/GZR 12 weeks. The evidence presented supports the use of EBR/GZR in patient groups considered difficult to treat (prior treatment failures), those who are co-infected with HIV and HCV, and in those who are considered to have high unmet clinical need (CKD, stage 4-5). Additionally, EBR/GZR was shown to be highly efficacious and safe in the treatment of patients in receipt of OST, which in the majority of cases were using illicit drugs. These data have real world implications, as the PHE 2015 report suggests that ~50% of current PWIDs are infected with HCV, and ~90% of new HCV infections are in PWIDs. In addition to the high rates of SVR12 observed, the safety and tolerability of EBR/GZR has also been established vs. control and active treatment with SOF+PR. Data suggests that the use of RBV can impact both the frequency and severity of AEs experienced leading to treatment discontinuation. Therefore, EBR/GZR represents a valuable treatment option for HCV patients, and in particular those described above.

The results of HRQoL considered in the health economic model indicate that no on-treatment decrements were observed for patients treated with EBR/GZR relative to worsening in HRQoL in patients treated with IFN-containing regimens.

4.13.2 Discussion of the strengths and limitations of the clinical evidence base for the technology

Many of the challenges that were faced in producing comparisons between EBR/GZR and the other NICE recommended treatments stem from there being few head-to-head trials and a large number of non-randomised single-arm trials. The use of imputed arms within NMA to get around this issue is relatively novel and subject to some limitations. The analysis would have been strengthened by adjusting the imputed PR responses according to the

characteristics of the populations from the non-comparative trials. However, this was not possible as baseline patient information was not available for the subgroups on which the analysis was conducted. Yet the use of these subgroups, selected for their influence on treatment response, means that the effect of any true differences between populations is likely to be minimal. This is, in part, reflected by the high degree of consistency between the direct comparisons and indirect estimates from the NMA. Consistency could have been more thoroughly explored through a method known as 'edge splitting' but no closed loops were available with which to carry this out.

The numerical flexibility of the Bayesian framework within which the NMA was carried out represents a strength of this analysis. Bayesian methods do not lead to different estimates compared to what would be obtained through frequentist methods; however, they permit the simplification of large correlation structures, which otherwise risk leading to convergence issues within the optimisation algorithms used by maximum likelihood methods. In addition, Bayesian methods mean estimates can be derived from a single, coherent model rather than a sequence of models.

It should be recognised that the number of included trials and patients were very low in some analyses. In some instances, this was due to lack of trials being carried out in specific patient groups, while in others it was the result of data from trials not being presented in such a way that allowed its inclusion within the evidence synthesis. This required several assumptions to be made (e.g. the use of GT1 data as a proxy for GT4), and thus, some results may be less precise than others. Additionally, sparse data meant that it was not possible to conduct NMA for some safety outcomes.

4.14 Ongoing studies

A comprehensive list of clinical trial records (n=50) relevant to GT1 and GT4 infections, identified via ICTRP, is described in Appendix 8.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Strategies used to retrieve cost-effectiveness studies relevant to decision-making in England

Relevant cost-effectiveness studies were identified through a SLR search performed between 13 and 19 October 2015, and updated on 20 January 2016, for patients with chronic HCV. Given the evolving landscape in chronic HCV treatment over the last decade, electronic database searches and additional hand-searches were restricted to the last 10 years, as cost data older than that are not considered representative of the current economic environment.

The following research questions were posed in accordance with the decision problem:

- What is the cost-effectiveness of EBR/GZR and comparator therapies in treating patients with chronic HCV?
- What is the HRQoL (in terms of utilities) associated with chronically infected HCV patients?
- What are the resource requirements and costs associated with the treatment of chronic HCV?

A comprehensive literature search relative to these three research questions was carried out using several databases:

- MEDLINE and EMBASE (using EMBASE.com) – 2005 to October 2015 – searches updated in January 2016
- MEDLINE In-Process (using PubMed.com) – searches updated in January 2016
- EconLit: January 2005 to October 2015 – searches updated in January 2016
- Tufts: Cost-effectiveness Analysis Registry: https://research.tufts-nemc.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx
- The Cochrane Library, including the following:
    - National Health Services-Economic Evaluation Database (NHS-EED)
    - Centre for Reviews and Dissemination (CRD)-HTA Database

In addition, the NICE website was searched to identify relevant information from previous submissions not otherwise captured. A bibliographic search of the relevant, published

systematic reviews, economic models and HTAs was also conducted to ensure that all studies of relevance to the review had been captured in the initial searches.

Conference searches were also performed to identify potentially relevant conference posters or abstracts of interest. These searches were constrained to the most recent 2 years because it is expected that any abstracts published prior to that would have been published as full-text articles by this time. These searches covered the following conferences:

- European Association for the Study of the Liver (EASL): http://www.easl.eu/
- American Association for the Study of the Liver Disease (AASLD): http://www.aasld.org/
- European Congress of Clinical Microbiology and Infectious Diseases (ESCMID): https://www.escmid.org/research_projects/eccmid/
- Viral Hepatitis Congress: http://viral-hep.org/
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European Congress: http://www.ispor.org/meetings/PastEuro.aspx; ISPOR Annual International Congress: http://www.ispor.org/meetings/PastInternational.aspx

All retrieved studies were reviewed by two independent researchers and assessed against the eligibility criteria set out in the final protocol and are presented in Table 57.

Table 57. Inclusion and exclusion criteria for cost-effectiveness studies

Criteria	Inclusion	Exclusion	Rationale
Population	Adults (age ≥18 years) with HCV with or without any co-morbidity (except HIV)	• Healthy volunteers • Children (age <18 years) • HCV+HIV* • Disease other than HCV**	Relevant patient population
Intervention/comparator	Studies assessing at least one of the interventions listed below: • EBR/GZR • BOC+IFN+RBV*** • DCV+RBV • DCV+SOF • LDV/SOF • OMV/PRV/RTV with or without DSV • IFN+RBV • SMV+IFN+RBV • SOF+RBV • TVR+IFN+RBV***	• Studies that do not assess at least one of the included interventions are excluded • Studies are excluded on the basis of comparator therapy	To allow all papers with relevant interventions and all comparators to be captured

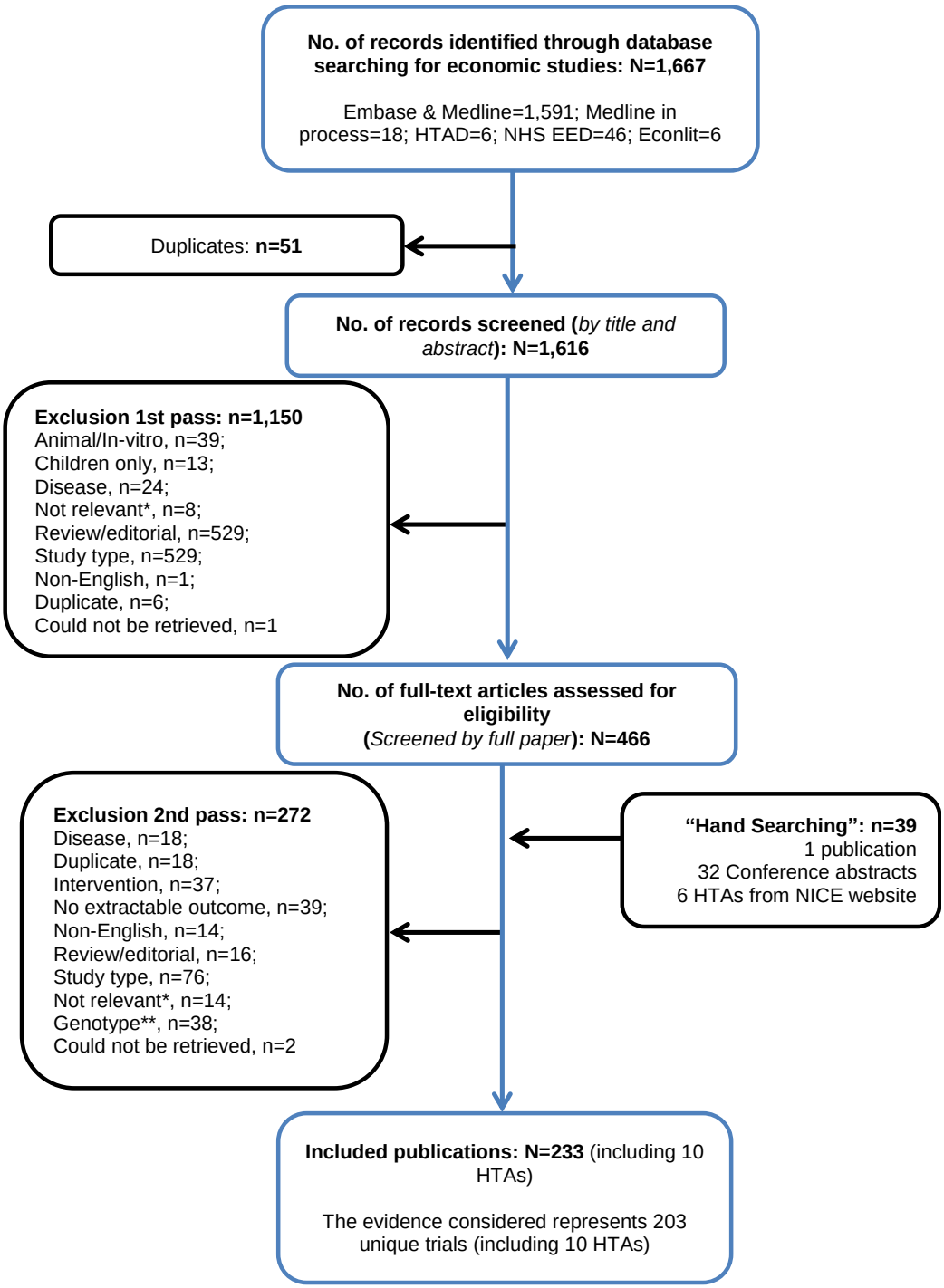
Criteria	Inclusion	Exclusion	Rationale
Outcomes	• ICER • Costs (unit and total) • QALYs • LYs • Incremental costs • Incremental QALYs/LYs • Model inputs (e.g. transition probabilities, % of patients at fibrosis stage etc.) • Sensitivity analyses results	No specific exclusion criteria	To identify relevant cost-effectiveness studies
Study type	Full economic evaluations, such as: • Cost–consequence • Cost-minimisation • Cost-effectiveness • Cost–utility • Cost–benefit	Non-systematic reviews****, letters and comment articles. Burden of illness studies and non-modelling will be excluded	To identify primary study articles and relevant cost-effectiveness studies
Language	• Studies published in English • Studies published in non-English languages were included and flagged*****	Studies were not excluded on the basis of publication language	To ensure that all relevant information were captured
Time horizon	From 1 January 2005 to 20 January 2016		

Abbreviations. BOC: boceprevir; DCV: daclatasvir; DSV: dasabuvir; EBR: elbasvir; GZR: grazoprevir; HCV, hepatitis C virus infection: HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; IFN: interferon; LDV: ledipasvir; Lys: life years; OMV: ombitasvir; PRV: paritaprevir; QALY: quality-adjusted life years; RBV: ribavirin; RTV: ritonavir; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir.

Notes: *, HIV is a devastating disease which severely affects the patients' immune system therefore patients co-infected with HCV and HIV may incur higher costs while their QoL is severely impaired by the co-infection ; **, studies assessing patients with HCV-related liver cancer were included and flagged; ***, studies evaluating BOC+IFN+RBV or TVR+IFN+RBV were included only if these therapies were evaluated against PEG-IFN+RBV either alone or in combination with other protease inhibitors; ****, systematic reviews were included and flagged for bibliography searches; *****, studies published in languages other than English were explored only if sufficient evidence was not identified from English studies.

The search strategy is provided in Appendix 12. A total of 1,667 articles were retrieved by the search (1,530 references were identified from the initial search and 137 from the updated search in January 2016). After removal of 51 duplicates, preliminary screening of abstracts and titles was performed on 1,616 records against the criteria outlined in Table 57, and 1,150 papers were excluded. The majority of records were excluded on the basis of review/editorial (529) and study type (529). After preliminary screening, 466 records were included for full publication review. Following review of the full texts, 233 publications (of these, 14 publications were identified by updated searches) were included and relevant data were extracted from 203 unique studies. The remaining 30 publications sourced their data from the same original publication. The number of included full-publications and conference abstracts was 94 and 139, respectively. The PRISMA flow diagram is presented in Figure 15.

Figure 15. PRISMA flow diagram for cost-effectiveness studies



Abbreviations. HCV: hepatitis C virus; HTA: health technology assessments; HTAD: Health Technology Assessment Database; NHS EED: NHS Economic Evaluation Database; PEG-IFN: pegylated interferon; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBV: ribavirin.
Note: *, BOC or TVR studies that do not assess PEG-IFN+RBV either alone or in combination with other protease inhibitors or where the comparator therapy was unclear, including those studies which compare early or delayed treatment approach of BOC or TVR therapies, were excluded on the exclusion code non-relevant studies; **, Studies that do not assess HCV patients with GT1 and/or GT4 were excluded on exclusion code genotype.

5.1.2 Brief overview of each cost-effectiveness study only if it is relevant to decision-making in England

The evidence tabulated in the main body of this report is solely focussed on included UK studies (n=32) since they represent the most relevant data inputs required for an economic model reflecting costs and benefits from a UK perspective. Other studies conducted outside the UK have been tabulated in Appendix 13.

A summary list of published UK cost-effectiveness studies is compiled in Table 58.

Table 58. Study characteristics and outcomes reported in the identified cost-effectiveness studies conducted in the UK

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
Shepherd et al., 2005 [109]	CEA	Type: Markov cohort (n=1,000) model; Health states: Chronic HCV; progression to cirrhosis; development of ascites, variceal bleeds, hepatic encephalopathy; HCC, LT, and death	UK NHS	• PEG-IFN+RBV • IFN+RBV	TN with chronic moderate to severe HCV infection with genotype 1,2,3,4,5,6	30-year period	**Discounted QALYs:** • IFN+RBV (48 weeks): 23,098 • PEG-IFN+RBV (48 weeks): 23,417 **Discounted QALYs for patient genotype subgroups:** Genotype 1[a] • IFN+RBV (48 weeks): 22,743 • PEG-IFN+RBV (48 weeks): 23,098 Genotype 4, 5 or 6[b] • IFN+RBV (48 weeks): 22,814 • PEG-IFN+RBV (48 weeks): 23,240 [a] - based on SVR reported in Fried et al; [b] - based on SVR reported in Manns et al.	**Total discounted costs:** • IFN+RBV (48 weeks): £9,987,505 • PEG-IFN+RBV (48 weeks): £13,862,982 **Total discounted costs for patient genotype subgroups:** Genotype 1[a] • IFN+RBV (48 weeks): £10,192,934 • PEG-IFN+RBV (48 weeks): £14,046,070 Genotype 4, 5 or 6[b] • IFN+RBV (48 weeks): £10,151,848 • PEG-IFN+RBV (48 weeks): £13,964,698 [a] - based on SVR reported in Fried et al; [b] - based on SVR reported in Manns et al.	**PEG-IFN+RBV vs IFN+RBV for 48 weeks**: £12,123 **PEG-IFN+RBV vs IFN+RBV for 48 weeks for patient genotype subgroups:** Genotype 1[a] £10,848 Genotype 4, 5 or 6[b] £8,946 [a] based on SVR reported in Fried et al; [b] based on SVR reported in Manns et al.

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
Grieve et al., 2006 [110]	CEA	Type: Markov model Health states: Mild-moderate disease, moderate disease-cirrhosis, cirrhosis-DCC, cirrhosis or DCC-HCC, DCC-death, HCC-death, all cause death	Health service perspective	• PEG-IFN-2b+RBV • NT	Patients with mild chronic HCV; 60% men; 50% genotype 1; 50% genotype non-1	Lifetime (up to 50 years for patients entering the model aged 40 years)	**Base case results (mean QALYs):** • PEG-IFN-2b+RBV: Genotype 1 (15.17); Genotype non-1 (15.79) • NT: Genotype 1 (14.99); Genotype non-1 (15.18) **Mean lifetime QALY for different treatment strategies:** • Mild disease: NT; moderate disease: IFN-2b+RBV = Genotype 1 (14.99); Genotype non-1 (15.18) • Mild disease: IFN-2b+RBV; moderate disease: NT = Genotype 1 (15.17); Genotype non-1 (15.79) • Mild disease: NT; moderate disease: PEG-IFN-2b+RBV = Genotype 1 (15.03); Genotype non-1 (15.21)	**Base case results (mean cost):** • PEG-IFN-2b+RBV: Genotype1 (£14,833); Genotype non-1 (£11,343) • NT: Genotype1 (£10,472); Genotype non-1 (£8,561) **Mean lifetime cost for different treatment strategies:** • Mild disease: NT; moderate disease: IFN-2b+RBV = Genotype 1 (£10,472); Genotype non-1 (£8,561) • Mild disease: IFN-2b+RBV; moderate disease: NT = Genotype 1 (£14,883); Genotype non-1 (£11,343) • Mild disease: NT; moderate disease: PEG-IFN-2b+RBV = Genotype 1	**Genotype 1 patients (mean cost/QALY):** Difference between PEG-IFN-2b+RBV and NT: £25,188 ($39,480) **Genotype non-1 patients (mean cost/QALY):** Difference between PEG-IFN-2b+RBV and NT: £4,535 ($ 7,108)

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
							• Mild disease: PEG-IFN-2b+RBV; moderate disease: NT=Genotype 1 (15.29); Genotype non-1 (15.91)	(£11,581); Genotype non-1 (£9,630) • Mild disease: PEG-IFN-2b+RBV; moderate disease: NT = Genotype 1 (£18,897); Genotype non-1 (£15,084)	
Wright et al., 2006[23]	CEA (HTA document)	Type: Markov model Health states: SVR, Mild-Moderate disease, Cirrhosis, HCC, DCC, Liver transplant, death	Health service perspective	• PEG-IFN-2b+RBV (48 weeks) • NT	TN adult patients with mild CHC, ; 60% men; 40%women 50% genotype 1, 50% non-1	Lifetime (up to 50 years for patients entering the model aged 40 years)	**Lifetime QALYs:** • PEG-IFN-2b+RBV:15.47 • NT: 15.09 **Base case QALY gained:** Genotype 1:0.17 Genotype Non-1: 0.61 **Mean lifetime QALY for different treatment strategies:** • Mild disease: NT; moderate disease: PEG-IFN-2b+RBV = Genotype 1 (14.99); Genotype non-1 (15.18)	**Lifetime costs (£):** • PEG-IFN-2b+RBV: £13,199 • NT: £9,552 **Base case Incremental cost (£):** Genotype 1: 4,361 Genotype Non-1: 2,782 **Mean lifetime cost for different treatment strategies:** • Mild disease: NT; moderate disease: PEG-IFN-2b+RBV = Genotype 1 (£10,472);	**Lifetime ICER Overall :** PEG-IFN-2b+RBV vs NT: £9,535 **Genotype 1 patients (mean cost/QALY):** Difference between PEG-IFN-2b+RBV and NT: £25,188 **Genotype non-1 patients (mean cost/QALY):** Difference between PEG-IFN-2b+RBV and NT: £4,535

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
							• Mild disease: PEG-IFN-2b+RBV; moderate disease: NT = Genotype 1 (15.17); Genotype non-1 (15.79) • Mild disease: NT; moderate disease: PEG-IFN-2b+RBV = Genotype 1 (15.03); Genotype non-1 (15.21) • Mild disease: PEG-IFN-2b+RBV; moderate disease: NT=Genotype 1 (15.29); Genotype non-1 (15.9)	Genotype non-1 (£8,561) • Mild disease: PEG-IFN-2b+RBV; moderate disease: NT = Genotype 1 (£14,883); Genotype non-1 (£11,343) • Mild disease: NT; moderate disease: PEG-IFN-2b+RBV = Genotype 1 (£11,581); Genotype non-1 (£9,630) • Mild disease: PEG-IFN-2b+RBV; moderate disease: NT = Genotype 1 (£18,897); Genotype non-1 (£15,084)	
Shepherd et al., 2007[111]	CEA (HTA document)	Type: Markov state transition model Health states : mild HCV, moderate HCV, CC, HCC, DCC,	UK NHS and Personal Social Services	• PEG-IFN-2a/2b+RBV (48 weeks)IFN-2a/ • 2b+RBV (48 weeks) • BSC	Adults with mild chronic HCV with genotype 1, 2 & 3	Life time	Genotype 1 **IFN-2b+RBV for 18% SVR** Watchful waiting: 20.33 Early treatment: 20.66 **IFN-2b+RBV for 30% SVR**	Genotype 1 **IFN-2b+RBV for 18% SVR** Watchful waiting: £9,074 Early treatment: £14,297 **IFN-2b+RBV for 30% SVR**	**Watchful waiting with IFN+RBV versus BSC:** £7,766–ICER: 19,022 **Early treatment with IFN+RBV versus watchful waiting with IFN+RBV care:** £9,021–15,954 **Watchful waiting with**

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
		LT					Watchful waiting: 20.51 Early treatment: 21.06 **PEG-IFN-2a+RBV** Watchful waiting: 20.65 Early treatment: 21.38 **PEG-IFN-2b+RBV** Watchful waiting: 20.84 Early treatment: 21.82 **BSC**: 27.94	Watchful waiting: £8,641 Early treatment: £13,640 **PEG-IFN-2a+RBV** Watchful waiting: £9,293 Early treatment: £16,799 **PEG-IFN-2b+RBV** Watchful waiting: £9,143 Early treatment: £17,273 **BSC:**£5,989	**PEG-IFN- 2a+RBV versus BSC:** £6,867 **Early treatment with PEG-IFN-2a+RBV versus watchful waiting with PEG-IFN-2a+RBV:** £10,270 **Watchful waiting with PEG-IFN-2b+RBV versus BSC:**£4,670 **Early treatment with PEG-IFN-2b+RBV versus watchful waiting with PEG-IFN-2b+RBV:** £8,324
Grishnchenko et al., 2009 [112]	CEA	Type: Markov model Health states: Mild disease, moderate disease, cirrhosis, AVT, SVR, DCC, HCC, liver transplant, post liver transplant	Health service perspective	• PEG-IFN+RBV • No AVT	Genotype 1 HCV patients; genotype non-1 HCV patients	NR	Mean QALYs: **Mild HCV** *Genotype 1:* • PEG-IFN + RBV: 15.78 • No AVT: 14.67 *Genotype non-1:* • PEG-IFN + RBV: 16.25 • No AVT: 14.20 **Moderate HCV**	Mean costs: **Mild HCV** *Genotype 1:* • PEG-IFN+RBV: £16,104 • No AVT: £12,228 *Genotype non-1:* • PEG-IFN+RBV: £10,750 • No AVT: £15,362 **Moderate HCV**	ICER for PEG-IFN+RBV vs no AVT for: **Mild HCV** *Genotype 1:* £3,507 *Genotype non-1:* AVT dominates **Moderate HCV** *Genotype 1:* AVT dominates *Genotype non-1:* AVT

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
		state, liver related death					*Genotype 1:* • PEG-IFN+RBV: 12.59 • No AVT: 11.64 *Genotype non-1:* • PEG-IFN+RBV: 13.43 • No AVT: 11.15 **Cirrhosis** *Genotype 1:* • PEG-IFN+RBV: 8.12 • No AVT: 7.71 *Genotype non-1* • PEG-IFN+RBV: 9.45 • No AVT: 7.71	*Genotype 1:* • PEG-IFN+RBV: £29,122 • No AVT: £30,044 *Genotype non-1* • PEG-IFN+RBV: £17,250 • No AVT: £32,442 **Cirrhosis** *Genotype 1:* • PEG-IFN+RBV: £47,709 • No AVT: £44,476 *Genotype non-1:* • PEG-IFN+RBV: £34,977 • No AVT: £44,539	dominates **Cirrhosis** *Genotype 1:* £8,017 *Genotype non-1:* AVT dominates
Jensen et al., 2009[113]	CEA	Type: Markov model Health states: NR	UK health care payer perspective	• PEG-IFN-2a+RBV (72 weeks) • PEG-IFN-2a+RBV (48 weeks) • NT	HCV mono-infected patients with genotype 1	Lifetime	• NR	• Incremental costs of PEG-IFN-2a+RBV (72 weeks) vs PEG-IFN-2a+RBV (48 weeks): £606 • Incremental costs of PEG-IFN-2a+RBV (72 weeks) vs NT: £1,949	• PEG-IFN-2a+RBV (72 weeks) vs. PEG-IFN-2a+RBV (48 weeks): £2,012/QALY • PEG-IFN-2a+RBV (72 weeks) vs. NT: £2,988/QALY
Hartwell et	CEA	Type:	UK NHS and	• PEG-IFN-	Adults with	Life time	**Non-responders &**	**Non-responders &**	**BSC vs PEG-IFN-2a for**

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
al.,2011[26]	(HTA document)	Markov model Health states: SVR, Mild HCV, Moderate HCV, CC, HCC, DCC, LT & Death.	Personal Social Services	2a/2b+RBV • PEG-IFN 2a/2b • BSC • PEG-IFN-2a+RBV (standard dose of 24 or 48 weeks)	chronic HCV with genotype 1, 2, 3 and 4		**relapsers with PEG-IFN-2a+RBV** Genotype 1 BSC: 10.74 PEG-IFN-2a: 11.05 Genotype non-1 BSC: 10.74 PEG-IFN-2a: 11.33 **Non-responders & relapsers with PEG-IFN-2b+RBV** Genotype 1 &4 BSC: 10.74 PEG-IFN-2a: 11.14 **Shortened treatment duration with PEG-IFN-2a+RBV**: Genotype 1[a] IFN+RBV (48 weeks): 15.68 IFN+RBV (24 weeks): 15.54 Genotype 1[b] IFN+RBV (48 weeks): 15.68 IFN+RBV (24 weeks): 15.60 **Shortened**	**relapsers with PEG-IFN-2a+RBV** Genotype 1 BSC: £26,221 PEG-IFN-2a: £42,350 Genotype non-1 BSC: £26,221 PEG-IFN-2a: £32,640 **Non-responders & relapsers with PEG-IFN-2b+RBV** Genotype 1 &4 BSC: £26,221 PEG-IFN-2a: £35,601 **Shortened treatment duration with PEG-IFN-2a+RBV**: Genotype 1[a] IFN+RBV (48 weeks): £14,206 IFN+RBV (24 weeks): £9,399 Genotype 1[b] IFN+RBV (48 weeks): £14,206 IFN+RBV (24 weeks): £8,994 **Shortened**	**non-responders & relapsers with PEG-IFN-2a+RBV** Genotype 1: £52,587 Genotype non-1: £10,926 **BSC vs PEG-IFN-2a for non-responders & relapsers with PEG-IFN-2b+RBV** Genotype 1 &4: £23,912 **PEG-IFN+RBV (48 weeks) vs IFN+RBV (24 weeks)** Genotype 1[a]: £34,510 Genotype 1[b]: £64,880 **PEG-IFN+RBV (48 weeks) vs IFN+RBV (24 weeks)** Genotype 1[c]: IFN+RBV (24 weeks) dominates [a] - based on Liu and colleagues 2008 [b] - based on Yu and colleagues 2008 [c] - based on Berg and colleagues 2009

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
							treatment duration with PEG-IFN-2b+RBV: Genotype 1[c] IFN+RBV (48 weeks): 13.89 IFN+RBV (24 weeks): 14.38 [a] - based on Liu and colleagues 2008 [b] - based on Yu and colleagues 2008 [c] - based on Berg and colleagues 2009	**treatment duration with PEG-IFN-2b+RBV** : Genotype 1[c] IFN+RBV (48 weeks): £26,169 IFN+RBV (24 weeks): £17,173 [a] - based on Liu and colleagues 2008 [b] - based on Yu and colleagues 2008 [c] - based on Berg and colleagues 2009	
NICE, 2011a [TA253] [39]	CEA (HTA document)	Type: Markov model Health states: F0-4, SVR F0, SVR F1, SVR F2, SVR F3, F4, CC SVR, DCC, HCC, LT (first year), liver related death, post LT.	UK NHS and Personal Social Services	• BOC+PEG-IFN+RBV • PEG-IFN+RBV	TN & TE adults with chronic HCV with genotype 1	Lifetime (100 years)	**BOC+PEG-IFN+RBV** • TN: 15.30 • TE: 14.47 **PEG-IFN+RBV** • TN : 14.38 • TE : 12.48	**BOC+PEG-IFN+RBV** • TN: £32,699 • TE : £38,339 **PEG-IFN+RBV** • TN : £22,128 • TE : £32,861	**BOC+PEG-IFN+RBV vs PEG-IFN+RBV** • TN: £10,570 • TE: £5,478
NICE, 2011b [TA252] [38]	CEA (HTA document)	Type: Markov model Health states: SVR, mild HCV,	UK NHS and Personal Social Services	• TVR+PEG-IFN+RBV • PEG-IFN+RBV	TN & TE adults with chronic HCV with genotype 1	Life time (70 years)	**TVR+PEG-IFN+RBV** • TN: 13.87 • TE: 11.26 **PEG-IFN+RBV**	**TVR+PEG-IFN+RBV** • TN: £36,152 • TE: £44,589 **PEG-IFN+RBV**	**TVR+PEG-IFN+RBV vs PEG-IFN+RBV** • TN: £13,553 • TE: £8,688

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
		moderate HCV, CC, HCC, DCC, LT.					• TN: 13.03 • TE: 10.09	• TN: £24,722 • TE: £34,394	
Nikoglou et al.,2011[114]	CEA	Type: Markov model Health states: NR	NHS, Scotland	• BOC RGT • Full duration BOC arm (4 weeks PEG-IFN+RBV plus 44 weeks triple therapy) • PEG-IFN+RBV (standard arm; 48 week)	HCV patients with genotype 1	NR	• NR	• NR	The ICER over current SOC lies between £6,462 and £13,299 for TN patients and between £5,248 and £6,684 for TE patients, depending on treatment duration
Cure et al., 2012[115]	CEA	Type: Markov model Health states: NR	NHS Scotland	**TN:** • TVR (12 weeks)+PEG-IFN+RBV (for 24 weeks to patients achieving an eRVR and 48 weeks to patients not achieving an eRVR) **TE:** • TVR (12	Genotype 1 HCV infected patients	NR	• NR	• NR	• Higher costs and improved outcomes associated with TVR+PEG-IFN+RBV relative to PEG-IFN+RBV alone, resulting in an ICER: ○ TN**:** £14,230 ○ TE: £9,440 • The ICER of the prior relapse, prior partial responder and prior null-responder sub-populations, were £5,363, £10,558 and £27,725, respectively.

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
				weeks)+PEG-IFN+RBV (for 48 weeks)					
Curtis et al., 2012[116]	CEA	Type: Markov model Health states: NR	NHS	**TN:** TVR RGT [12 weeks of TVR with PEG-IFN+RBV (24 weeks for patients achieving an eRVR and 48 weeks for patients not achieving an eRVR)] **TE:** TVR (12 weeks)+PEG-IFN+RBV (48 weeks)	Genotype 1 HCV infected patients	NR	• NR	• NR	• Introduction of TVR to current SOC for HCV genotype 1 was cost-effective compared to PEG-IFN+RBV alone at the £20,000 and £30,000 willingness-to-pay thresholds for both TN and TE patients regardless of IL-28B subtypes
Hartwell et al., 2012[117]	CEA	Type: Markov Model Health states: NR	UK NHS and PSS	PEG-IFN+RBV (shortened [24 weeks for genotype 1; vs standard duration)	Adults with chronic HCV (genotype 1,2/3) who were eligible for shortened treatment (i.e., with	Lifetime	**For PEG-IFN-2a+RBV:** For genotype 1, shortened treatment duration is associated with an overall QALY loss (between 0.08 and 0.14). **For PEG-IFN-**	**For PEG-IFN-2a+RBV:** For genotype 1 patients, shortened duration (24 weeks) of treatment is associated with a reduction in total costs between approximately £4,800	**For PEG-IFN-2a+RBV:** For genotype 1 ICERs range from £34,150 to £64,880. **For PEG-IFN-2b+RBV:** For genotype 1, shortened duration treatment dominates over standard duration

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
					baseline LVL and an RVR at week 4 of treatment)		**2b+RBV:** There was a QALY gain of 0.49 due to a higher SVR in shortened treatment duration; therefore this strategy dominated standard treatment	and £5,200. **For PEG-IFN-2b+RBV:** Shorter duration of treatment was associated with a reduction in total costs of approximately £9,000	treatment but ICER was not reported
Humphreys et al., 2012[118]	CEA	Type: Markov model Health states: NR	NHS and PSS	• BOC+PEG-IFN+RBV • PEG-IFN+RBV	TN and TE patients with genotype 1 chronic HCV	Lifetime	• NR	• NR	**TN:** BOC+PEG-IFN+RBV vs PEF-IFN+RBV: £11,601. **TE:** BOC+PEG-IFN+RBV vs PEF-IFN+RBV: £2,909.
Jacobson et al., 2012[119]	CEA	Type: NR Health states: NR	NR	PEG-IFN+RBV+TVR, (TVR for 12 weeks and PEG-IFN+RBV for 24 or 48 weeks)	Genotype 1 HCV-infected patients with F2 fibrosis	NR	• NR	• NR	TVR was associated with higher costs relative to PEG-IFN+RBV, resulting in an ICER of £9,930/QALY.
Thorlund et al., 2012[120]	BIA	Type: Primary model: Bayesian Markov model Health states: N/A	Patient & Societal	• BOC+PEG-IFN+RBV • PEG-IFN+RBV+TVR *standard of care: PEG-IFN+RBV	HCV mono-infected patients with genotype 1	NR	N/A	**Total average cost for TN and TE patients were:** • RGT with BOC: £22,850 and £25,060 • RGT with TVR: £29,930 and	• N/A

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
								£31,880 • Standard-duration BOC: £34,680 and £34,350 • Standard duration TVR: £32,530 and £31,680	
McEwan et al., 2013[121]	CUA	Type: Markov cohort simulation model; MONARCH Health states: SVR, chronic HCV, fibrosis stage F4 (CC), DCC, HCC and LT	Payer's	• Standard duration therapy (PEG-IFN-2a+RBV); 48 weeks • RGT (time to first undetectable HCV-RNA; 72 weeks • NT	Chronic HCV genotype1, 45-year old patients with a 20-year history of HCV infection (1:1 male and female).	Lifetime	Standard duration therapy and RGT was associated with an increase of 2.14 and 2.20 QALYs, respectively, compared to NT.	Standard duration therapy and RGT was associated with an increase of £2,374 and £2,270 costs, respectively, compared to NT.	Overall, RGT was a dominant scenario being associated with a lower risk of complications, increased QALYs (0.08) and cost saving (£104). RGT across fibrosis stages was either highly cost effective or dominant.
Cure et al., 2014a[122]	CEA	Type: Markov model Health states: Mild and moderate fibrosis, CC, DCC, HCC, LT and post-LT	NHS	• TVR+PEG-IFN-2a+RBV • PEG-IFN+RBV alone • BOC+PEG-IFN+RBV	TN patients with chronic HCV genotype 1 infection	Lifetime time (up to 100 years of age)	**Total QALYs:** • TVR+PEG-IFN-2a+RBV: 13.89 • PEG-IFN+RBV: 13.03 • BOC+PEG-IFN-2b+RBV: 13.68	**Total costs:** • TVR+PEG-IFN-2a+RBV: £35,347 • PEG-IFN+RBV: £24,420 • BOC+PEG-IFN-2b+RBV: £38,105	**TVR+PEG-IFN-2a+RBV vs PEG-IFN+RBV** Incremental costs: £10,927 Incremental QALYs: 0.86 **ICER (cost per QALY gained):** £12,733 for TVR+PEG-IFN-2a+RBV vs BOC+PEG-IFN-2b+RBV
Cure et	CEA	Type:	NHS	• TVR+PEG-	TE patients	Lifetime	**All patients:**	**All patients:**	**TVR+PEG-IFN-2a+RBV**

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
al.,2014b[123]		Markov model Health states: Mild and moderate fibrosis, CC, DCC, HCC, LT and post-LT		IFN-2a+RBV • PEG-IFN+RBV alone • BOC+PEG-IFN+RBV	with chronic HCV genotype 1 infection	time (up to 100 years of age)	• TVR+PEG-IFN-2a+RBV: 11.24 • PEG-IFN+RBV: 10.08 • BOC+PEG-IFN-2b+RBV: NA **Relapsers:** • TVR+PEG-IFN-2a+RBV: 11.96 • PEG-IFN+RBV: 10.48 • BOC+PEG-IFN-2b+RBV: 11.45 **Partial responders:** • TVR+PEG-IFN-2a+RBV: 11.17 • PEG-IFN+RBV: 10.11 • BOC+PEG-IFN-2b+RBV: 11.28 **Null responders** • TVR+PEG-IFN-2a+RBV: 9.87 • PEG-IFN+RBV: 9.28 • BOC+PEG-IFN-2b+RBV: NA	• TVR+PEG-IFN-2a+RBV: £44,855 • PEG-IFN+RBV: £37,810 • BOC+PEG-IFN-2b+RBV: NA **Relapsers:** • TVR+PEG-IFN-2a+RBV: £38,918 • PEG-IFN+RBV: £34,977 • BOC+PEG-IFN-2b+RBV: £52,878 **Partial responders:** • TVR+PEG-IFN-2a+RBV: £45,932 • PEG-IFN+RBV: £37,891 • BOC+PEG-IFN-2b+RBV: £53,619 **Null responders:** • TVR+PEG-IFN-2a+RBV: £55,705 PR: £43,291 • BOC+PEG-IFN-2b+RBV: NA	**vs PEG-IFN+RBV** **All patients:** • ICER (cost per QALY gained): £6,079 **Relapsers:** • ICER (cost per QALY gained): £2,658 **Partial responders:** • ICER (cost per QALY gained): £7,593 **Null responders:** • ICER (cost per QALY gained): £20,875 **TVR+PEG-IFN+RBV vs BOC+PEG-IFN+RBV** **All patients:** • ICER (cost per QALY gained): NA **Relapsers:** • ICER (cost per QALY gained): TVR+PEG-IFN+RBV dominates **Partial responders:** • ICER (cost per QALY gained): TVR+PEG-IFN+RBV is less costly and less efficacious **Null responders:** • ICER (cost per QALY

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
									gained): NA
Miners et al., 2014 [124]	CEA	Type: Markov model Health states: DCC, HCC, LT, Post- LT	National Health Service (NHS)	• PEG-IFN+RBV • NT	Genotype 1, genotype 2/3	Lifetime horizon	• PEG-IFN+RBV: 17.762 • NT: 17.759	• PEG-IFN+RBV: £425 • NT: £373	Approximately £23,200.
Westerhout et al., 2014[125]	CUA	Type: Markov model Health states: NR	UK NHS	• PEG-IFN+RBV+SMV • PEG-IFN+RBV • PEG-IFN+RBV+TVR • BOC+PEG-IFN+RBV	Patients with HCV infection of genotype 1 and 4	Life time	• NR	• NR	**Genotype 1:** • PEG-IFN+RBV+SMV vs PEG-IFN+RBV for **TN:** £14,206/QALY • PEG-IFN+RBV+SMV vs PEG-IFN+RBV for **TE:** £9,793/QALY • PEG-IFN+RBV+SMV dominated PEG-IFN+RBV+TVR and BOC+PEG-IFN+RBV in both patient groups. **Genotype 4:** • PEG-IFN+RBV+SMV vs PEG-IFN+RBV for **TN**: £20,791/QALY and £11,662/QALY • PEG-IFN+RBV+SMV vs PEG-IFN+RBV for **TE**: £12,070/QALY and £8,896/QALY
Cure et al., 2015b [126]	CEA	Type: Markov model	NHS in the UK	• PEG-IFN-2a+RBV+SOF (12	HCV mono-infected patient with	NR	• NR	**Genotype 1 TN interferon eligible (costs difference):**	**Genotype 1 TN interferon eligible:**

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
		Health states: Non-cirrhotic, cirrhotic, HCV, DCC, HCC, LT		weeks or 24 weeks) • PEG-IFN-2a+RBV+TVR • BOC+PEG-IFN-2b+RBV • PEG-IFN-2a+RBV (48 weeks) • RBV+SOF • NT	genotype 1, 2/3, and 4/5/6			• SOF+PEG-IFN-2a+RBV (12 weeks) vs TVR+PEG-IFN-2a+RBV: £5,288 • SOF+PEG-IFN-2a+RBV(12 weeks) vs BOC+PEG-IFN-2b+RBV: £4,902 • SOF+PEG-IFN-2a+RBV (12 weeks) vs PEG-IFN2a+RBV (48 weeks): £19,129	• SOF+PEG-IFN-2a+RBV (12 weeks) vs TVR+PEG-IFN-2a+RBV: £11,836 • SOF+PEG-IFN-2a+RBV(12 weeks) vs BOC+PEG-IFN2b+RBV: £7,292 • SOF+PEG-IFN2a+RBV (12 weeks) vs PEG-IFN2a+RBV (48 weeks): £14,930 **Genotype 1 TN unsuitable for interferon:** SOF+RBV (24 weeks) vs NT: £49,249 **Genotype 4/5/6 TN:** SOF+PEG-IFN-2a+RBV (12 weeks) vs PEG-IFN-2a+RBV (48 weeks): £26,797
Dillon et al., 2015 [127]	CEA	Type: Markov Model Health states: Non-cirrhotic , cirrhotic, LT, liver-related mortality	NR	• LDV/SOF (8, 12 or 24 weeks) • PEG-IFN+RBV+SOF (12 or 24–48 weeks) • PEG-IFN+RBV+S	Chronic HCV patients with genotype 1 or 4.	NR	In chronic HCV genotype 1 TN patients, treatment with LDV/SOF led to greater QALYs achievement, compared to SOF+PEG-IFN+RBV and SMV+PEG-IFN+RBV (values	In chronic HCV genotype 1 TN patients, treatment with LDV/SOF was associated with cost savings compared to SOF+PEG-IFN+RBV and SMV+PEG-IFN+RBV (values were not reported)	• In chronic HCV genotype 1 TN, LDV/SOF dominated SOF+PEG-IFN+RBV and SMV+PEG-IFN+RBV. • In genotype 4 TN patients, LDV/SOF was cost-effective

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
				MV (12 or 24–48 weeks)			were not reported)		compared to SOF+PEG-IFN+RBV with an ICER of £4,088 • In genotype 4 TN patients, LDV/SOF was cost-effective compared to SMV+PEG-IFN+RBV with an ICER of £12,651 • In TE genotype 1 and GT4 patients, LDV/SOF had ICERs of £5,894 compared to SOF+PEG-IFN+RBV and £9,788 compared to SMV+PEG-IFN+RBV.
Howells R, 2015 [128]	CEA	Type: Markov model Health states: Non-cirrhotic or cirrhotic disease state, SVR, DCC, HCC and LT or death.	NR	• LDV+SOF • NT • Current treatment options	TN and TE patients with chronic HCV genotype 1 or 4.	Lifetime	• NR	• NR	• In GT1 TN patients without cirrhosis (8 weeks LDV/SOF treatment) and GT4 TN patients without cirrhosis (12 weeks LDV/SOF treatment), LDV/SOF was cost effective for all comparators with ICERs of £8,894 and £22,676 versus the next most effective non-dominated option, respectively.

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
									• In GT1 or GT4 TN patients with cirrhosis, TE patients without cirrhosis, and TE patients with cirrhosis, 12 week LDV/SOF was associated with ICERs of £4,518, £16,566, and £5,435 versus NT, respectively; • All active comparators were dominated or extendedly dominated.
McEwan et al., 2015d [129]	CEA	Type: Markov model Health states: NR	NR	• DCV+SOF • PEG-IFN+RBV+TVR • BOC+PEG-IFN+RBV • PEG-IFN+RBV+SMV • PEG-IFN+RBV • NT	TN, TE and IFN-ineligible/intolerant patients with HCV genotype 1 advanced disease (METAVIR score ≥F3), mean age of 50 years; 67% male.	Lifetime	• NR	**Weekly treatment costs:** • DCV: £2,083.1 • SOF: £2,915.2 • SMV: £1,866.5 • RBV: £66.95 • PEG-IFN+RBV: £191.35	ICER (£) for DCV+SOF versus **Data for TN:** • SOF+PEG-IFN+RBV: 14,240 • SMV+PEG-IFN+RBV: 12,265 • PEG-IFN+RBV: 8,861 • NT: 4,263 **Data for TE:** NT: 4,263
McEwan et al., 2015e [130]	CEA	Type: Markov model Health states: NR	NR	• DCV+SOF • PEG-IFN+RBV+TVR • NT	HCV genotypes 1, 3 and 4 patients with advanced	Lifetime	**Genotype 1: Incremental QALYs** • DCV+SOF vs TVR+PEG-IFN+RBV: 1.95	**Genotype 1: Incremental costs** • DCV+SOF vs TVR+PEG-IFN+RBV: £15,282	**Genotype 1:** • DCV+SOF vs TVR+PEG-IFN+RBV: £7,830 • DCV+SOF vs NT:

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
					disease (METAVIR score ≥ F3), mean age 50 years; 67% male.		• DCV+SOF vs NT: 4.88 **Genotype 4:** QALYs gains for • PEG-IFN+RBV: 3.07 • NT: 5.36	• DCV+SOF vs NT: £20,798 **Genotype 4:** Incremental cost for • PEG-IFN+RBV: £26,966 • NT: £18,636	£4,263 **Genotype 4:** • DCV+SOF vs PEG-IFN+RBV: £8,782 • DCV+SOF vs NT: £3,477
NICE, 2014a [TA364] [12]	CEA (HTA document)	Type: Decision tree & Markov model Health states: SVR, F0-F4; DCC, HCC, LT & death.	UK NHS and Personal Social Services	• PEG-IFN+RBV • NT • SMV+PEG-IFN+RBV • TVR+PEG-IFN+RBV • SOF+PEG-IFN+RBV • BOC+PEG-IFN+RBV • DCV+SOF • SMV+SOF • SOF+RBV • DCV+PEG-IFN+RBV	TN, TE & IFN ineligible/intolerant adults with chronic HCV with genotype 1, 3 & 4.	Life time (80 years)	**Genotype 1 patients** **TN** DCV+SOF (vs SMV) Fibrosis*:13.68 CC:13.61 DCV+SOF (vs SOF) Fibrosis*: 13.68 DCV+SOF (vs other) Fibrosis*: 13.68 SMV+PEG-IFN+RBV Fibrosis*: 12.07 CC: 11.02 SOF+PEG-IFN+RBV Fibrosis*: 12.72 CC:12.33 PEG-IFN+RBV Fibrosis*: 10.70 CC: 9.69 NT Fibrosis*: 8.80 CC: 7.14 **TE** DCV+SOF Fibrosis*: 13.68 CC: 13.61	**Genotype 1 patients** **TN** DCV+SOF (vs SMV) Fibrosis*: £61,188 CC: £121,215 DCV+SOF (vs SOF) Fibrosis*: £61,188 DCV+SOF (vs other) Fibrosis*: £61,188 SMV+PEG-IFN+RBV Fibrosis*: £41,049 CC: £47,208 SOF+PEG-IFN+RBV Fibrosis*: £46,313 CC: £48,237 PEG-IFN+RBV Fibrosis*: £32,181 CC : £36,089 NT Fibrosis*: £40,389 CC: £46,719 **TE** DCV+SOF Fibrosis*: £61,188 CC: £121,215	**Genotype 1 patients; ICERs for DCV+SOF vs the interventions listed below** **TN** SMV+PEG-IFN+RBV Fibrosis*: £12,547 CC: £28,563 SOF+PEG-IFN+RBV Fibrosis*: £15,584 CC: £56,812 PEG-IFN+RBV Fibrosis*: £9,749 CC: £21,705 NT Fibrosis*: £4,263 CC: £11,506 **TE** SOF+PEG-IFN+RBV Fibrosis*: No data CC: No data NT Fibrosis*: £4,263 CC: £11,506

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
							SOF+PEG-IFN+RBV Fibrosis*: No data CC: No data NT Fibrosis*: 8.80 CC: 7.14 **Genotype 4 patients** ***DCV+ PEG-IFN+RBV comparison population*** **TN** DCV+PEG-IFN+RBV Fibrosis*: 12.55 CC: 12.07 SMV+PEG-IFN+RBV Fibrosis*: 12.72 CC: 12.48 SOF+PEG-IFN+RBV Fibrosis*: 13.65 CC: 10.37 PEG-IFN+RBV Fibrosis*: 10.63 CC: 8.66 NT Fibrosis*: 8.32 CC: 7.14 **TE** DCV+PEG-IFN+RBV Fibrosis*: 12.55 CC: 12.07	SOF+PEG-IFN+RBV Fibrosis*: No Data CC: No data NT Fibrosis*: £40,389 CC: £46,719 **Genotype 4 patients** ***DCV+ PEG-IFN+RBV comparison population*** **TN** DCV+PEG-IFN+RBV Fibrosis*: £59,256 CC: £61,749 SMV+PEG-IFN+RBV Fibrosis*: £35,825 CC: £36,890 SOF+PEG-IFN+RBV Fibrosis*: £38,760 CC: £61,814 PEG-IFN+RBV Fibrosis*: £31,920 CC: £43,454 NT Fibrosis*: £42,552 CC: £46,719 **TE** DCV+PEG-IFN+RBV Fibrosis*: £59,256 SMV+PEG-IFN+RBV Fibrosis*: £56,818	**Genotype 4 patients** ***DCV+ PEG-IFN+RBV comparison population*** **TN** SMV+PEG-IFN+RBV Fibrosis*: -£143,992 CC: -£60,760 SOF+PEG-IFN+RBV Fibrosis*: -£18,647 CC: -£38 PEG-IFN+RBV Fibrosis*: £14,223 CC: £5,367 NT Fibrosis*: £3,945 CC: £3,046 **TE** SMV+PEG-IFN+RBV Fibrosis*: £1,237 CC: £1,103 SOF+PEG-IFN+RBV Fibrosis*: No data CC: No data PEG-IFN+RBV Fibrosis*: £4,001 CC: £3,220 NT Fibrosis*: £3,945 CC: £3,046 ***DCV+SOF comparison population*** **TN** SMV+PEG-IFN+RBV

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
							SMV+PEG-IFN+RBV Fibrosis*: 10.58 CC: 9.89 SOF+PEG-IFN+RBV Fibrosis*: No data CC: No data PEG-IFN+RBV Fibrosis*: 9.11 CC: 8.12 NT Fibrosis*: 8.32 CC: 7.14 ***DCV+SOF comparison population*** **TN** DCV+SOF Fibrosis*: 13.68 CC: 13.61 SMV+PEG-IFN+RBV Fibrosis*: 12.72 CC: 12.48 SOF+PEG-IFN+RBV Fibrosis*: 13.65 CC : 10.37 PEG-IFN+RBV Fibrosis*: 10.63 CC: 8.66 NT Fibrosis*: 8.32 CC: 7.14 **TE**	CC: £61,749 SOF+PEG-IFN+RBV Fibrosis*: No data CC: £59,338 PEG-IFN+RBV Fibrosis*: £45,478 CC: £49,009 NT Fibrosis*: £42,552 CC: £46,719 ***DCV+SOF comparison population*** **TN** DCV+SOF Fibrosis*: £61,188 CC: £121,215 SMV+PEG-IFN+RBV Fibrosis*: £35,825 SOF+PEG-IFN+RBV Fibrosis*: £38,760 CC: £61,814 PEG-IFN+RBV Fibrosis*: £31,920 CC: £43,454 NT Fibrosis*: £42,552 CC: £46,719 **TE** DCV+SOF Fibrosis*: £61,188 CC: £121,215	Fibrosis*: £26,358 CC: £74,602 SOF+PEG-IFN+RBV Fibrosis*: £868,019 CC: £18,313 PEG-IFN+RBV Fibrosis*: £9,606 CC: £15,714 NT Fibrosis*: £3,477 CC: £11,506 **TE** SMV+PEG-IFN+RBV Fibrosis*: £1,411 CC: £16,605 SOF+PEG-IFN+RBV Fibrosis*: No data CC: No data PEG-IFN+RBV Fibrosis*: £3,439 CC: £13,137 NT Fibrosis*: £3,477 CC: £11,506 **Note:** *patients with significant fibrosis (F3 to F4 non-cirrhotic)

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
							DCV+SOF Fibrosis*: 13.68 CC: 13.61 SMV+PEG-IFN+RBV Fibrosis*: 10.58 CC: 9.89 SOF+PEG-IFN+RBV Fibrosis*: No data CC: No data PEG-IFN+RBV Fibrosis*: 9.11 CC: 8.12 NT Fibrosis*: 8.32 CC: 7.14 **Note:** *patients with significant fibrosis (F3 to F4 non-cirrhotic)	SMV+PEG-IFN+RBV Fibrosis*: £56,818 CC: £59,338 SOF+PEG-IFN+RBV Fibrosis*: No data CC: No data PEG-IFN+RBV Fibrosis*: £45,478 CC: £49,009 NT Fibrosis*: £42,552 CC: £46,719 **Note:** *patients with significant fibrosis (F3 to F4 non-cirrhotic)	
NICE, 2014b [TA363] [11]	CEA (HTA document)	Type of model: Markov model Health States: Non-cirrhotic, SVR non-cirrhotic, SVR cirrhotic, CC, HCC, DCC, Liver transplant, post liver transplant, excess	NHS and personal social services perspective	• LDV+SOF • SOF+PEG-IFN-a+RBV • SMV+PEG-IFN-2a+RBV • PEG-IFN-2a+RBV • TVR+PEG-IFN-2a+RBV • BOC+PEG-IFN-2a+RBV • NT • SMV+SOF	• Genotype 1 TN • Genotype 4 TN • Genotype 1 & 4 TE • Genotype 3 TN and TE (unsuitable for IFN therapy), HCV patients	Lifetime time horizon	**TN- Genotype (1) Genotype (4) And TE- Genotype (1 & 4)** **Total QALYs** • NT: (13.01) (13.01) and (12.40) • PEG-IFN-2a+RBV: (13.98) (13.98) and (12.75) • LDV+SOF: (15.66) (15.67) and (14.72) • SMV+PR: (15.02) (15.02) and (14.13)	**TN Genotype (1) Genotype (4) And TE – Genotype (1 & 4)** **Total Costs (£)** • NT: (£18,956) (£18,956) and (£18,143) • PEG-IFN-2a+RBV: (£25,308) (£25,308) and (£24,960) • LDV+SOF:	**Base-case cost-effectiveness results (ICER for LDV/SOF ± RBV against each comparator £/QALY)** **Genotype 1-TN** • LDV/SOF vs. SOF+PEG-IFN-2a+RBV: LDV/SOF dominates • LDV/SOF vs. SMV+PEG-IFN-2a+RBV: LDV/SOF dominates • LDV/SOF vs. PEG-IFN-2a+RBV: £7,985

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
		mortality					• SOF+PR: (15.40) (15.40) and (14.21) **Incremental (versus no treatment) QALYS :** • PEG-IFN-2a+RBV: (0.97) (0.97) and (0.35) • LDV+SOF: (2.65) (2.66) and (2.32) • SMV+PR: (2.01) (2.01) and (1.73) • SOF+PR : (2.39) (2.39) and (1.81)	(£38,713) (£46,823) and (£49,537) • SMV+PR: (£38,731) (£38,731) and (£43,626) • SOF+PR: (£45,776) (£45,776) and (£46,756) **Incremental (versus no treatment) Costs (£) :** • PEG-IFN-2a+RBV: (£6,352) (£6,352) and (£6,817) • LDV+SOF: (£19,757) (£27,867) and (£31,395) • SMV+PR: (£19,774) (£19,774) and (£25,483) • SOF+PR : (£26,819) (£26,819) and (£28,613)	• LDV/SOF vs. NT: £7,458 **Genotype 4-TN** • LDV/SOF vs. SOF+PEG-IFN2a+RBV: £3,869 • LDV/SOF vs. SMV+ PEG-IFN-2a+RBV: £12,399 • LDV/SOF vs. PEG-IFN-2a+RBV: £12,715 • LDV/SOF vs. NT: £10,468 **Genotype 1 and 4 -TE** • LDV/SOF vs. SOF+PEG-IFN-2a+RBV: £5,497 • LDV/SOF vs. SMV+ PEG-IFN-2a+RBV: £9,984 • LDV/SOF vs. PEG-IFN-2a+RBV: £12,491 • LDV/SOF vs. TVR+PEG-IFN-2a+RBV : £9,144 • LDV/SOF vs. BOC+PEG-IFN-2a+RBV: £3,551 • LDV/SOF vs. NT: £13,527 **ICER (£/QALY) versus no treatment for TN HCV Genotype-(1) (4)**

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
									and TE HCV-(1 & 4) • PEG-IFN-2a+RBV: (£6,548) (£6,548) and (£19,292) • LDV+SOF: (£7,458) (£10,468) and (£13,527) • SMV+PR: (£9,840) (£9,840) and (£14,740) • SOF+PR: (£11,215) (£11,215) and (£15,765) **ICER (£/QALY) Incremental for TN HCV G-(1) (4) And TE HCV-(1 & 4)** • PEG-IFN-2a+RBV: (£6,548) (£6,548) and (Extended dominance) • LDV+SOF: (£7,985) (£12,715) and (£13,527) • SMV+PR: (Dominated) (Extended dominance) and (Extended dominance) • SOF+PR : (Dominated) (Extended dominance) and (Extended dominance)
NICE, 2014c	CEA (HTA docum	Type: Markov model	UK NHS and Personal Social	• OMV+PRV+ RTV+DSV • OMV+PRV+	TN & TE adults with chronic	Lifetime (70	**Genotype 1, TN, IE patients** • PEG-IFN+RBV:	**Genotype 1, TN, IE patients** • PEG-IFN+RBV:	**Genotype 1, TN, IE patients; ICER vs PEG-**

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
[TA365] [13]	ent)	Health states: SVR mild HCV, SVR moderate HCV, SVR CC, mild HCV, moderate HCV, CC, HCC, DCC, LT and death.	Services	RTV • BOC+PEG-IFN+RBV • TVR+PEG-IFN+RBV • SOF+PEG-IFN+RBV • PEG-IFN+RBV • NT	HCV with genotype 1 & 4.	years)	13.72 • OMV+PRV+RTV+DSV: 15.21 • SOF+PEG-IFN+RBV: 15.01 **Genotype 1, TE (overall), IE patients** • PEG-IFN+RBV: 11.07 • OMV+PRV+RTV+DSV: 13.19 **Genotype 4, TN, IE (non-cirrhotic only) patients** • PEG-IFN+RBV: 15.00 • OMV+PRV+RTV: 15.84 • SOF+PEG-IFN+RBV: 15.81 **Genotype 4, TE, IE (non-cirrhotic only) patients** • NT: 12.58 • OMV+PRV+RTV: 14.84	£22,872 • OMV+PRV+RTV+DSV: £43,624 • SOF+PEG-IFN+RBV: £44,337 **Genotype 1, TE (overall), IE patients** • PEG-IFN+RBV: £30,128 • OMV+PRV+RTV+DSV: £51,882 **Genotype 4, TN, IE (non-cirrhotic only) patients** • PEG-IFN+RBV: £19,286 • OMV+PRV+RTV: £36,490 • SOF+PEG-IFN+RBV: £41,237 **Genotype 4, TE, IE (non-cirrhotic only) patients** • NT: £16,186 • OMV+PRV+RTV: £36,536	**IFN+RBV** • OMV+PRV+RTV+DSV: £13,864 • SOF+PEG-IFN+RBV: Dominated **Genotype 1, TE (overall), IE patients; ICER vs PEG-IFN+RBV** • OMV+PRV+RTV+DSV: £10,258 **Genotype 4, TN, IE (non-cirrhotic only) patients; ICER vs PEG-IFN+RBV** • OMV+PRV+RTV: £20,351 • SOF+PEG-IFN+RBV: Dominated **Genotype 4, TE, IE (non-cirrhotic only) patients; ICER vs NT** • OMV+PRV+RTV: £8,977
NICE, 2014d [TA330] [10]	CEA (HTA docum ent)	Type: Markov model Health States: Non-cirrhosis , Cirrhosis, CC,	NHS and Personal Social Services perspective	**Genotype 1 TN, IE:** • SOF+PEG-IFN-2a+RBV (12 weeks) • NT	• TN patients with HCV genotype 1 infection, including	Lifetime horizon	**Total QALYs:** **Genotype 1 TN, IE:** • PEG-IFN-2a+RBV (48 weeks): 13.8 • SOF+PEG-IFN-2a+RBV (12	**Total Costs (£):** **Genotype 1 TN, IE:** • PEG-IFN-2a+RBV (48 weeks): £24,994 • SOF+PEG-IFN-	**ICER incremental (QALYs) :** **Genotype 1 TN, IE:** • SOF vs. PEG-IFN-2a+RBV: £14,930

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
		DCC, HCC, Liver and post-liver transplant, Excess mortality		• PEG-IFN-2a+RBV (48 weeks) • TVR+PEG-IFN-2a+RBV (24-48 weeks) • BOC+PEG-IFN-2b+RBV (28-48 weeks) **Genotype 1 TN, unsuitable for IFN:** • SOF+RBV (24 weeks) • NT	who are IFN eligible or unsuitable for IFN • TN and TE patients with HCV genotype 2 & genotype 3 infection, including who are IFN eligible or unsuitable for IFN • TN genotype 4, 5 or 6 HCV Patients		weeks): 15.1 **Incremental QALY:** **Genotype 1 TN, IE:** • PEG-IFN-2a+RBV (48 weeks): NA • SOF+PEG-IFN-2a+RBV (12 weeks): 1.3	2a+RBV (12 weeks): £44,123 **Incremental costs (£):** **Genotype 1 TN, IE:** • PEG-IFN-2a+RBV (48 weeks): NA • SOF+PEG-IFN-2a+RBV (12 weeks): £19,129	**ICER incremental (QALYs) :** **Genotype 1 TN, IE:** • PEG-IFN-2a+RBV (48 weeks): NA • SOF+PEG-IFN-2a+RBV (12 weeks): £14,930
Westerhout et al., 2015[131]	CEA	Type: Markov model Health states: SVR F0/F2: Y1, SVR F3:	NHS in England	1. No NS5A resistance-testing and all patients received LDV ± RBV+SOF	Chronic HCV patients with genotype 1	Lifetime	1. No NS5A resistance-testing and all patients received LDV ± RBV+SOF according to the European label	1. No NS5A resistance-testing and all patients received LDV ± RBV+SOF according to the European label	**ICER (£/QALY)* for treatment strategies:** 1. Testing LDV+SOF 12 weeks if NS5A+: £15,288 2. Testing LDV/SOF 24

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
		Y1, SVR F4: Y1-5, F0/F2, F3, F4, DCC, HCC, LT, post- LT, death (all cause)		2. Pre-treatment testing followed by 12 weeks SOF+SMV in patients with NS5A resistance and label-based SOF+LDV±RBV in patients without NS5A resistance. 3. Pre-treatment testing followed by optimized (24 weeks) LDV ± RBV+SOF in NS5A resistant patients and label-based SOF+LDV±RBV for patients without NS5A resistance.			(12 weeks for F0-F3 patients, 24 weeks for F4 patients): Total QALYs: 15.74 2. Pre-treatment testing followed by 12 weeks SOF+SMV in patients with NS5A resistance and label-based LDV/SOF ± RBV in patients without NS5A resistance: Total QALYs: 15.87; Incremental QALYs: 0.127 3. Pre-treatment testing followed by optimized (24 weeks) LDV ± RBV+SOF in NS5A resistant patients and label-based LDV/SOF ± RBV for patients without NS5A resistance: Total QALYs: 15.89; Incremental QALYs: 0.020	(12 weeks for F0-F3 patients, 24 weeks for F4 patients): Total costs: £ 43,062 2.Pre-treatment testing followed by 12 weeks SOF+SMV in patients with NS5A resistance and label-based LDV/SOF ± RBV in patients without NS5A resistance: Total costs: £45,002; Incremental costs: £1,940 3. Pre-treatment testing followed by optimized (24 weeks) LDV ± RBV+SOF in NS5A resistant patients and label-based LDV/SOF ± RBV for patients without NS5A resistance: Total costs: £47,765; Incremental costs: £2,762	weeks if NS5A+: £ 138,028 *ICERs presented for the following comparisons: £138,028 for strategy 3) vs. 2), £15,288 for strategy 2) vs. 1). NS5A+: population with NS5A resistance. No NS5A testing has the highest probability of being cost-effective for a WTP threshold up to £15,500 per QALY gained; testing followed by LDV+SOF 12 weeks in NS5A resistant patients has the highest probability for WTPs of £15,500 and higher.
McEwan et al., 2016[132]	CEA	Type: Markov model Health states: SVR, F0-4,	UK NHS and Personal Social Services	• TVR+ PEG-IFN+RBV • BOC+ PEG-IFN+RBV	HCV patients with genotypes	Life time horizon	NR	NR	**HCV genotype 1 (DCV+SOF):** **TN:**

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
		DCC, HCC, LT (year 1 & year 2+) & death Cohort (1000 patients) across fibrosis stages F3 (78.6 ± 2.8%) and F4 (21.4 ± 5.4%)		• SMV+ PEG-IFN+RBV • SMV+ SOF • SOF +RBV • DCV+ PEG-IFN+RBV • DCV+SOF • NT	1 and 4 and a METAVIR score of F3–F4. The percentage of men (67 ± 0.4%) and mean age (50 ± 0.2 years). Three patient types were considered in the analysis: • TN • TE (including previous relapsers, null responders and partial responders) • IFN ineligible or intolerant				• **SMV +PEG-IFN+RBV:** £13,577 • **SOF+PEG-IFN+RBV:** £57,410 • **PEG-IFN+RBV:** £10,550 • **NT:** £4,600 **TE:** • **NT:** £4,600 **HCV genotype 4 (DCV+SOF comparison):** **TN:** • **SMV +PEG-IFN+RBV:** £28,393 • **PEG-IFN+RBV:** £10,356 • **NT:** £3,762 **TE:** • **SMV +PEG-IFN+RBV:** £1,539 • **PEG-IFN+RBV:** £3,715 • **NT:** £3,762 **HCV genotype 4 (DCV+PR comparison):** **TN:** • **SMV +PEG-IFN+RBV:** £-151,581 (DCV dominated) • **PEG-IFN+RBV:** £15,408

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
									• **NT:** £4,291 **TE:** • **SMV +PEG-IFN+RBV:** £1,394 • **PEG-IFN+RBV:** £4,348 • **NT:** £4,291

Abbreviations. AVT, antiviral therapy; BOC, boceprevir; BIA, budget impact analysis; BSC: best supportive care; CC, compensated cirrhosis; CEA, cost effectiveness analysis; CHC: Chronic hepatitis C; CUA, cost utility analysis; DAA, direct acting antivirals; DCC, Decompensated cirrhosis; DCV, daclatasvir; DSV, dasabuvir; DVR, delayed virological response; eRVR, extended rapid viral response; HCC, Hepatocellular carcinoma; HCV, hepatitis C virus; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; IFN, interferon; LDV, ledipasvir; LT, liver transplantation; LVL, low viral load; MONARCH, MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis; NHS, National Health Services; NR, not reported; NS5A, non-structural protein 5A; NT, no treatment; OMV, ombitasvir; PEG-IFN, pegylated interferon; PRV, paritaprevir; PSS, personal and social services; QALY, quality adjusted life years; RBV, ribavirin; RGT, response guided therapy; RNA, ribonucleic acid; RTV, ritonavir; RVR, rapid virological response; SDT, standard duration therapy; SMV, simeprevir; SOC: Standard of Care; SOF, sofosbuvir; SVR, sustained virological response; TE, treatment experienced; TN, treatment-naïve; TVR, telaprevir; WTP, willingness to pay.

5.1.3 Complete quality assessment for each relevant cost-effectiveness study identified

The quality of included cost-effectiveness studies was assessed using the checklist adapted from Drummond and Jefferson [133], in line with NICE reference case.

The complete quality assessment for each relevant cost-effectiveness study identified is presented in Appendix 14.

5.2 De novo analysis

5.2.1 Patient population

The patient population included in the economic evaluation reflects the anticipated EMA license: CHC with GT1a, GT1b and GT4 (see Appendix 1) and is in line with the population defined in the final scope. Although our expected EMA licensed does not distinguish patients by cirrhosis status and treatment history, NICE approved regimens are, in most cases, dependent on the aforementioned treatment characteristics. Thus, to facilitate any comparison, different subpopulations were considered and are presented in Table 59.

Table 59. Subpopulations included in the model

GT1a				GT1b				GT4			
TN		TE		TN		TE		TN		TE	
C	NC	C	NC	C	NC	C	NC	C	NC	C	NC

Abbreviations. C: cirrhotic; GT: genotype; NC: non-cirrhotic; TE: treatment experienced; TN: treatment naïve

GT4 is present in approximately 4% of HCV patients in the UK.[9] There is a limited number of GT4 HCV patients in EBR/GZR clinical trials (69/926 patients, 7.5% of all the EBR/GZR patients included in the NMA). When split by subgroups (as per Table 59), this is reduced even further which considerably limits the strength of the data available. MSD does not believe that this data is robust enough to inform the economic model in these specific subgroups. KOLs consulted supported the precedent set in previous NICE submissions, i.e. GT1 data could be used as a proxy for GT4 for the purpose of the economic evaluation. GT1 data in terms of SVR rates, discontinuation rates related to AEs and AEs, is therefore used as a proxy for GT4 in the base case scenario.

In the scenario analysis GT4 specific SVR, AEs and discontinuation rates are used in GT4 subgroups for EBR/GZR and comparators whenever available (see sections 5.8.3).

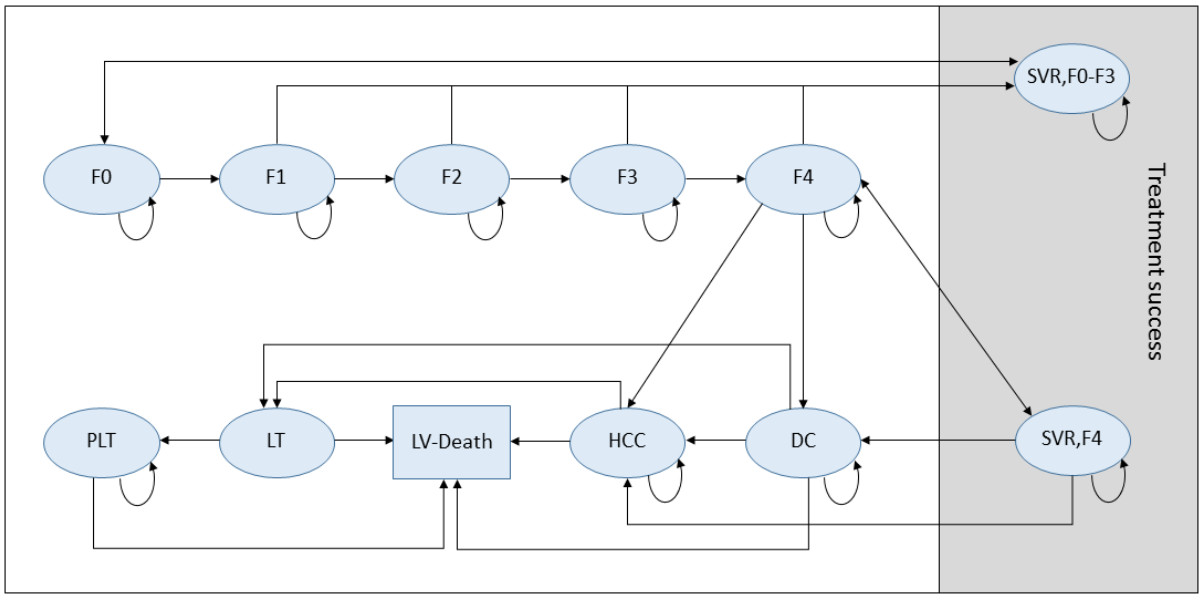
5.2.2 Model structure

A de novo Markov model was developed in Microsoft Excel®. It was designed to be consistent with the current understanding of the natural history of chronic HCV and to reflect

disease progression over the lifetime of a patient cohort (see Figure 16). The model takes into account the main efficacy outcome, SVR12, as evaluated in clinical trials. The structure of the model is similar to previously published models assessed in the UK and submitted to NICE in chronic HCV. [26, 111]

The state transition model consists of 13 health states (see Table 60 for full description of the health states). The severity of chronic HCV infection is described by the degree of fibrosis. In line with the results presented in the EBR/GZR post-hoc analyses, the results of the economic analysis are presented for the non-cirrhotic population (i.e. F0-F3 together) and the cirrhotic population (i.e. F4). This approach reflects current clinical practice informed by NICE TAs and CCP described in section 3. The same model structure is used for treatment naïve and treatment experienced patients with GT1a, GT1b and GT4 non-cirrhotic and cirrhotic.

Figure 16. Model structure



* The model consists of the following health states: no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), portal fibrosis with numerous septa without cirrhosis (F3), compensated cirrhosis (F4), decompensated cirrhosis (DC) states, hepatocellular carcinoma (HCC) state, two liver transplant states—first year (LT) and subsequent years: post liver transplant (PLT), liver-related death (LV-Death), death from all other causes (not shown here), and two sustained virologic response (SVR) status states stratified by fibrosis stage – 'SVR, F0–F3' and 'SVR, F4'. As shown by the double arrow lines, re-infection can occur from "SVR,F0-F3" to F0 and from "SVR,F4" to F4. The model assumes that patients cannot get re-infected from "SVR,F0-F3" to F1-F3.

Table 60. Description of the model health states

Health States	Description
F0	No fibrosis
F1	Portal fibrosis without septa
F2	Portal fibrosis with few septa
F3	Portal fibrosis with numerous septa without cirrhosis
F4	Compensated cirrhosis
SVR,F0-F3	F0-F3; achieved SVR after treatment
SVR,F4	Compensated cirrhosis; achieved SVR after treatment
DC	Decompensated cirrhosis
HCC	Hepatocellular carcinoma
LT	First year of liver transplant
PLT	After first year of liver transplant
LV-death	Liver-related death related to decompensated cirrhosis, HCC, or liver transplant

Abbreviations. SVR: sustained-virologic response

Patients are initiated on treatment in the first year of the model. Given the short durations of HCV treatments, all treatment-related outcomes occur within the first year of the model. In accordance with KOLs' opinion and in line with previous HCV models submitted to NICE [10-13, 40], the model assumes that chronically infected HCV patients cannot spontaneously clear their infection. In line with previous HCV models submitted to NICE, the model assumes that patients do not progress or die during the treatment period. [10-13, 40] After a successful treatment course, patients can achieve SVR, whereas those who do not achieve SVR are at risk of progressive liver disease, and are assumed to face the same risk of disease progression as untreated patients. At any stage patients can die of non-liver-related causes.

Patients enter the model in the non-cirrhotic or cirrhotic health states. In the non-cirrhotic health states, patients' initial distribution across fibrosis stages is characterised by Metavir Score F0 to F3 as per Hartwell et al 2011 publication. [26] The model assumes that a person with a given fibrosis score can remain in the current health state, achieve SVR, or progress onto more severe stages. Once patients progress to DC, HCC, LT or PLT health states they are at excess risk of liver-related death.

Non-cirrhotic patients who achieve SVR remain in the current health state unless re-infected. Cirrhotic patients who achieve SVR can either remain in the current health state or can progress onto more severe health states, and they are assumed to have an excess risk of DC and HCC. Patients with compensated cirrhosis (F4) can remain in the current health state, achieve SVR (i.e. "SVR,F4") or progress onto DC or HCC health states (Fattovich 1997). The DC health state consists of multiple outcomes (i.e. ascites, variceal haemorrhage

and encephalopathy); however, in accordance with KOLs opinion, given that the decompensation modes are not mutually exclusive, these have been combined into one health state.

Patients who develop DC may remain in the current health state, progress to HCC, receive liver transplant or die from liver-related death. [134] Patients with HCC can: remain in the current health state, progress and receive a liver transplant[135] [23] or die from liver-related causes [134].

Probability of mortality, costs and utilities are different immediately following transplantation (i.e. 1st year post transplant) when compared to later (i.e. post 1st year after transplant). For this reason the liver transplant health state has been divided into two separate states: LT and PLT. Patients alive at the end of the 1st year of liver transplant can move to the PLT health state or die from liver-related disease. [136] Patients who receive a liver transplant are assumed to be at no risk of reactivation of HCV and progression to liver disease (i.e. there are no risks for DC, HCC or need for re-transplantation).

5.2.3 Key features of the de novo analysis

Table 61. Key features of analysis

Factor	Chosen Value	Justification	Reference
Time horizon	Lifetime (up to age 100)	Lifetime horizon captures the long term differences in costs and health benefits between EBR/GZR and the comparators. This is in line with the NICE reference case.	NICE, 2013[137]
Cycle length	Annual	Assumption on annual cycle length is consistent with previous HCV models submitted to NICE.	Hartwell et al. 2011[26], Shepherd et al. 2007 [111], Grishchenko 2009[112].
Half-cycle correction	Included	Patients transition between health states throughout the cycle, and not only at the start and end of each cycle. This is consistent with previous HCV models submitted to NICE.	Hartwell et al. 2011[26] Shepherd et al. 2007[111]
Were health effects measured in QALYs; if not, what was used?	QALYs	This is consistent with previous HCV models submitted to NICE, and aligned with the NICE reference case.	NICE, 2013[137] Hartwell et al. 2011 [26] Shepherd et al. 2007 [111].
Discount of 3.5% for utilities and costs	3.5% for utilities and costs	This is consistent with previous HCV models submitted to NICE, and aligned with the NICE reference case.	NICE, 2013 [137] Hartwell et al. 2011 [26] Shepherd et al. 2007 [111].
Perspective (NHS/PSS)	NHS and PSS	This is consistent with previous HCV models submitted to NICE, and aligned with the NICE reference case.	NICE, 2013[137] Hartwell et al. 2011 [26] Shepherd et al.

Factor	Chosen Value	Justification	Reference
			2007 [111].

Abbreviations. NHS: National Health Service; NICE: National institute for health and care excellence; PSS: personal social services; QALY: quality-adjusted life year

5.2.4 Intervention technology and comparators

Relevant comparator regimens for EBR/GZR have been selected based on licensed indications and NICE recommendations, and are in line with the final scope. Table 62 lists the comparators chosen for the different patients subgroups.

Table 62. Main comparators included in the model

		Subgroups											
		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
Regimen	**Treatment duration (weeks)**	C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BSC	0		✓		✓		✓		✓		✓		✓
PR	48	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SOF+PR	12/12	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	
SMV+PR	12/24	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2D/3D	3D12RBV12		✓		✓	✓		✓					
	3D24RBV24	✓		✓									
	3D12						✓		✓				
	2D12RBV12										✓		✓
	2D24RBV24									✓		✓	
LDV/SOF	8		✓				✓						
	12	✓		✓	✓	✓		✓	✓	✓		✓	✓
DCV	DCV12SOF12		✓		✓		✓		✓				✓
	DCV24PR24									✓	✓	✓	✓

Abbreviations. 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; DCV: daclatasvir-based regimen; EBR: elbasvir; GT: genotype; GZR: grazoprevir; LDV: ledipasvir; NC: non-cirrhotic; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TE: treatment experienced; TN: treatment naïve

5.2.5 Discontinuation rules

Treatment durations for EBR/GZR and comparator products are based on EMA licenses. No included products are based on response guided therapy.

5.3 Clinical parameters and variables

5.3.1 Clinical data incorporated in the model

Clinical evidence supporting the economic model is presented in section 4.10 and is used to estimate the patients' baseline characteristics (e.g. age, sex, fibrosis score, weight, mortality rates), treatment characteristics (i.e. SVR rates), the proportion of patients experiencing AEs and the utilities used to populate the model (see Table 63). As mentioned in section 5.2.2, 100% of patients are either initially distributed across the F0-F3 state or enter in the cirrhotic health state. It is assumed that patients are distributed equally within the mild (F0-F1) and moderate states (F2-F3) (see Table 64). [26]

Table 63. Population characteristics and clinical data implemented in the model

	Data	Source
Population characteristics	Distribution of Metavir fibrosis stages at baseline	Hartwell et al 2011 [26]
	Mean age at baseline for TN and TE patients	Hartwell et al 2011 [26]
	Average weight	Hartwell et al 2011 [26]
	Gender distribution	Hartwell et al 2011 [26]
	Mortality rates	ONS lifetime table [138]
Treatment characteristics	SVR rates	EBR/GZR post-hoc analysis Comparators published literature (see section 4.10)
	Treatment duration	EBR/GZR post-hoc analysis NICE comparators TA guidance
	Discontinuation rates	EBR/GZR post-hoc analysis Comparators published literature (see section 4.10)
Adverse events	Rates of AEs	EBR/GZR post-hoc analysis Comparators published literature (see section 4.10)
Health related quality of life	Relative on-treatment decrement	EBR/GZR post-hoc analysis (EQ-5D) Comparators published literature (see section 5.4)

Abbreviations. AE: Adverse events; EBR/GZR: elbasvir/grazoprevir; EQ-5D: EuroQol-5 dimensions; ONS: Office for National Statistics; SVR: sustained-virologic response; TA: technology appraisal; TE: treatment-experience; TN: treatment-naïve

Population characteristics

Baseline characteristics of the modelled cohorts are sourced from Hartwell et al 2011, [26] which reports relevant UK population characteristics for treatment naïve and treatment experienced patients with CHC. The distribution of Metavir fibrosis stages at baseline is sourced from the same study.[26] As per the Metavir system, stages F0-F3 define the proportion of non-cirrhotic patients, whereas F4 defines the proportion of cirrhotic patients.

Age and gender specific all-cause mortality rates come from the Office for National Statistics (ONS) interim life tables in England. [138] The proportions of males/females, sourced from Hartwell et al. [26], are applied to the ONS mortality rates per gender [138] to calculate a weighted annual average mortality rate across gender. Patient characteristics are summarised in Table 64.

Table 64. Patient characteristics

Characteristic	Base case	Source
Mean age	TN: 40, TE: 45	Hartwell et al., 2011 [26]
% Male	70%	
Average weight	79kg	
Distribution of METAVIR fibrosis stage at baseline		
% F0	TN: 26.0%, TE: 24.0%	Hartwell et al., 2011 [26]
% F1	TN: 26.0%, TE: 24.0%	
% F2	TN: 24.0%, TE: 26.0%	
% F3	TN: 24.0%, TE: 26.0%	
% F4	TN: 100%, TE: 100%	

Abbreviations. F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis; TE, treatment experienced; TN, treatment naive

Treatment characteristics and adverse events

As detailed in section 4.10, a NMA of the published literature has been performed in order to identify the appropriate SVR, discontinuation related to AEs and AEs rates for EBR/GZR and for each of the comparators (Table 65, Table 66, Table 67). In the base case scenario, the NMA results, using the random effects model are implemented, whereas in scenario analysis the naïve indirect comparison results are applied (see Appendix 10). Relative risks (RR) are used in both the NMA and naïve indirect comparison to represent the relative efficacy and safety of EBR/GZR (based on absolute values) versus comparators.

EBR/GZR treatment duration is in line with the anticipated license. Comparators' treatment durations are informed from NICE TA recommendations and are summarised in Table 62. The NMA revealed no significant differences between EBR/GZR and the other all-DAA regimens (LDV/SOF, 2D/3D, and DCV+SOF) in any of the investigated subgroups.

- **SVR rates**

In the NMA, SVR results are estimated separately for GT1a and GT1b, therefore conservative assumptions were implemented to attribute SVR results for GT4 subgroups. In the base case scenario, for EBR/GZR, GT1a absolute SVR rates were applied whereas for the comparators, the lowest of GT1a and GT1b relative risks were implemented. For 2D/3D, GT1b data was used as a proxy for GT4. This is in line with TA363. [11] In scenario analysis, GT4 specific clinical inputs are applied (see Appendix 10).

- **Discontinuation rates**

Discontinuation rates related to AEs were modeled in line with occurrence of discontinuation reported in the clinical trials for EBR/GZR and comparators, when available. As discontinuation can occur at any time while on treatment, the model assumes that discontinuation occurs halfway through the treatment period (e.g. for EBR/GZR regimen where treatment duration is 12 weeks, patients who discontinue are assumed to stop the treatment at week 6). Consequently, the drug cost and HRQoL, attributed to patients discontinuing while on treatment, are adjusted. This is consistent with previous HCV models submitted to NICE [10-13, 40]. It is of note that EBR/GZR discontinuation rates are not available separately for GT1a and GT1b, therefore the same data has been implemented in both subgroups.

- **AEs rates**

The five key drug-related AEs, most commonly observed in EBR/GZR and comparators clinical trials, were modelled: anaemia, neutropenia, rash, pruritus and nausea. EBR/GZR clinical trials did not report these AEs according to severity (i.e. grade 3/4). We therefore considered these AEs overall for EBR/GZR and comparators. The level of data gathered for EBR/GZR and the comparators did not allow the AE results to be split between GT1a, GT1b and GT4; therefore, the overall GT1 data was applied to both GT1 and GT4 subgroups, according to cirrhotic state which was considered the main prognostic factor. [33]

Table 65. SVR rates for EBR/GZR and relative risk of EBR/GZR versus comparators based on the NMA – base case

Regimen	Treatment duration (weeks)	Subgroups SVR % (SE) for EBR/GZR and relative risk % (SE) of EBR/GZR versus comparators											
		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	96.2% (2.08%)	96.7% (0.86%)	91.1% (5.01%)	92.7% (3.61%)	100.0% (42.00%)	98.3% (0.86%)	100.0% (47.69%)	99.1% (2.04%)	96.2% (2.08%)	96.7% (0.86%)	91.1% (5.01%)	92.7% (3.61%)
BSC	0	SVR rates assumed to be 0%											
PR	48	2.68 (1.18)	1.86 (1.05)	4.03 (1.33)	2.28 (1.15)	2.89 (1.20)	1.92 (1.08)	3.58 (1.31)	2.58 (1.13)	2.68 (1.18)	1.86 (1.05)	3.58 (1.31)	2.28 (1.15)
SOF+PR	12/12	1.18 (1.67)	1.05 (1.12)	1.33 (2.46)	1.12 (1.27)	1.09 (1.46)	1.00 (1.03)	1.60 (2.84)	1.16 (1.37)	1.09 (1.46)		1.33 (2.46)	
SMV+PR	12/24	1.50 (1.39)	1.20 (1.07)	1.30 (2.21)	1.13 (1.32)	1.58 (1.52)	1.24 (1.09)	1.27 (2.18)	1.22 (1.53)	1.50 (1.39)	1.20 (1.07)	1.27 (2.18)	1.13 (1.32)
2D/3D	3D12RBV12		0.98 (1.03)		0.96 (1.09)	1.01 (1.14)		1.02 (1.54)					
	3D24RBV24	1.04 (1.18)		1.00 (1.49)									
	3D12						0.99 (1.02)		0.99 (1.08)				
	2D12RBV12										0.98 (1.03)		0.96 (1.09)
	2D24RBV24									1.01 (1.14)		1.00 (1.49)	
LDV/SOF	8		1.01 (1.05)				1.02 (1.07)						
	12	1.00 (1.05)		0.99 (1.18)	0.96 (1.08)	1.01 (1.05)		1.00 (1.15)	1.00 (1.05)	1.00 (1.05)		0.99 (1.18)	0.96 (1.08)
DCV	DCV12SOF12		0.98 (1.05)		0.97 (1.16)		1.00 (1.12)		1.00 (1.19)				0.97 (1.16)
	DCV24PR24									0.98 (1.05)	0.98 (1.05)	0.97 (1.16)	0.97 (1.16)

Abbreviations. 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; CIs: confidence intervals; DCV: daclatasvir-based regimen; EBR: elbasvir; GT: genotype; GZR: grazoprevir; LDV: ledipasvir; NC: non-cirrhotic; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained-virologic response; TE: treatment experienced; TN: treatment naïve

Table 66. Discontinuation rates for EBR/GZR and relative risks of EBR/GZR versus comparators based on the NMA – base case

Regimen	Treatment duration (weeks)	Subgroups SVR % (SE) for EBR/GZR and relative risk % (SE) of EBR/GZR versus comparators											
		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	0.42% (0.79%)	0.30% (0.26%)	0.42% (0.79%)	0.30% (0.26%)	0.42% (0.79%)	0.30% (0.26%)	0.42% (0.79%)	0.30% (0.26%)	0.42% (0.79%)	0.30% (0.26%)	0.42% (0.79%)	0.30% (0.26%)
BSC	0	Not applicable											
PR	48	0.02 (5.36)	0.06 (2.25)	0.02 (5.36)	0.06 (2.25)	0.02 (5.36)	0.06 (2.25)	0.02 (5.36)	0.06 (2.25)	0.02 (5.36)	0.06 (2.25)	0.02 (5.36)	0.06 (2.25)
SOF+PR	12/12	0.01 (5.64)	0.15 (3.68)	0.01 (5.64)	0.15 (3.68)	0.01 (5.64)	0.15 (3.68)	0.01 (5.64)	0.15 (3.68)	0.01 (5.64)		0.01 (5.64)	
SMV+PR	12/24	0.03 (6.05)	0.06 (5.30)	0.03 (6.05)	0.06 (5.30)	0.03 (6.05)	0.06 (5.30)	0.03 (6.05)	0.06 (5.30)	0.03 (6.05)	0.06 (5.30)	0.03 (6.05)	0.06 (5.30)
2D/3D	3D12RBV12		0.34 (2.74)		0.34 (2.74)	0.03 (6.69)		0.00 (6.69)					
	3D24RBV24	0.02 (6.35)		0.02 (6.35)									
	3D12						2.86 (4.72)		2.86 (4.72)				
	2D12RBV12										2.86 (4.72)		2.86 (4.72)
	2D24RBV24									0.03 (6.69)		0.02 (6.69)	
LDV/SOF	8		3.35 (4.39)				3.35 (4.39)						
	12	0.43 (6.10)		0.43 (6.10)	0.91 (4.22)	0.43 (6.10)		0.43 (6.10)	0.91 (4.22)	0.43 (6.10)		0.43 (6.10)	0.91 (4.22)
DCV	DCV12SOF12		1.14 (8.08)		1.14 (8.08)		1.14 (8.08)		1.14 (8.08)				1.14 (8.08)
	DCV24PR24									1.14 (8.08)	1.14 (8.08)	1.14 (8.08)	1.14 (8.08)

Key: 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; CIs: confidence intervals; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 67. Adverse event rates for EBR/GZR (SE) and relative risks of EBR/GZR versus comparators based on the NMA

Treatment	Aneamia	Nausea	Rash	Pruritus	Neutropenia
GT1 C					
EBR/GZR	0.4% (0.79%)	3.0% (1.16%)	3.0% (1.16%)	1.5% (1.01%)	0.4% (0.79%)
BSC	N/A	N/A	N/A	N/A	N/A
PR	0.01 (2.84)	0.25 (1.68)	0.09 (1.94)	0.08 (1.92)	0.01 (2.96)
SOF	0.01 (3.39)	0.17 (1.96)	0.18 (2.92)	0.17 (2.89)	0.04 (6.14)
SMV	0.01 (3.15)	0.21 (1.79)	0.08 (2.27)	0.07 (2.25)	0.01 (3.15)
3D/2D	0.02 (4.00)	0.26 (2.05)	0.16 (2.42)	0.32 (2.44)	0.01 (3.46)
LDV/SOF	0.39 (3.04)	0.85 (1.91)	0.47 (2.21)	0.58 (2.30)	0.00 (0.00)
DCV	N/A	N/A	N/A	N/A	N/A
GT1 NC					
EBR/GZR	0.1% (0.21%)	10.3% (1.02%)	2.2% (0.50%)	2.1% (0.48%)	0.2% (0.22%)
BSC	0	0	0	0	0
PR	0.02 (2.71)	0.40 (1.19)	0.10 (1.39)	0.05 (1.47)	0.01 (2.38)
SOF	0.03 (1.80)	0.63 (1.35)	0.28 (1.65)	0.24 (1.65)	0.01 (2.71)
SMV	0.02 (2.96)	0.41 (1.46)	0.12 (1.70)	0.06 (1.61)	0.01 (3.06)
3D/2D	0.06 (2.15)	0.59 (1.25)	0.31 (1.50)	0.17 (1.42)	0.64 (3.17)
LDV/SOF	0.81 (2.91)	1.65 (1.58)	2.08 (2.44)	3.14 (2.16)	0.00 (0.00)
DCV	0.67 (4.65)	0.50 (1.91)	0.73 (3.80)	2.38 (2.86)	0.03 (7.20)
GT4 C					
EBR/GZR	0.4% (0.79%)	3.0% (1.16%)	3.0% (1.16%)	1.5% (1.01%)	0.4% (0.79%)
BSC	N/A	N/A	N/A	N/A	N/A
PR	0.01 (2.84)	0.25 (1.68)	0.09 (1.94)	0.08 (1.92)	0.01 (2.96)
SOF	0.01 (3.39)	0.17 (1.96)	0.18 (2.92)	0.17 (2.89)	0.04 (6.14)
SMV	0.01 (3.15)	0.21 (1.79)	0.08 (2.27)	0.07 (2.25)	0.01 (3.15)
3D/2D	0.03 (2.40)	0.28 (2.04)	0.21 (2.40)	0.44 (2.44)	0.01 (3.46)
LDV/SOF	0.39 (3.04)	0.85 (1.91)	0.47 (2.21)	0.58 (2.30)	0.00 (0.00)
DCV	0.67 (4.65)	0.50 (1.91)	0.73 (3.8)	2.38 (2.86)	0.03 (7.20)
GT4 NC					
EBR/GZR	0.1% (0.21%)	10.3% (1.02%)	2.2% (0.50%)	2.1% (0.48%)	0.2% (0.22%)
BSC	0	0	0	0	0
PR	0.02 (2.71)	0.40 (1.19)	0.10 (1.39)	0.05 (1.47)	0.01 (2.38)
SOF	N/A	N/A	N/A	N/A	N/A
SMV	0.02 (2.96)	0.41 (1.46)	0.12 (1.70)	0.06 (1.61)	0.01 (3.06)
3D/2D	0.75 (2.51)	0.59 (1.38)	0.75 (1.63)	0.39 (1.49)	0.64 (3.17)
LDV/SOF	0.65 (3.17)	1.11 (1.44)	1.26 (2.16)	0.58 (2.032)	0.00 (0.00)
DCV	0.67 (4.65)	0.50 (1.91)	0.73 (3.80)	2.38 (2.86)	0.03 (7.20)

Abbreviations. AEs: adverse events; 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

5.3.2 Estimation of the proportion of patients by health state derived from the clinical data

The transition probabilities from non-cirrhotic (F0-F3) and cirrhotic (F4) health states to SVR health states (SVR F0-F3 and SVR F4) are based on SVR rates for EBR/GZR and RRs for comparator products as presented in section 5.3.1. The non-treatment specific transition probabilities used in the base case scenario are reported in Table 68. These are sourced from the literature, are in line with published cost-effectiveness models, and are reflective of the patient's probability of transitioning to more severe health state as the disease progresses.

Transition probabilities between F0-F4 used in our base-case model are based on the study by Thein et al [139], which is a systematic review and meta-analysis providing stage-specific progression rates by fibrosis-level. The results of the methodology employed in the study adjust for biases attributable to study design and selection factors associated with study population and clinical characteristics.

The study by Fattovich et al. 1997 [134], a natural history study of a cohort of 384 cirrhotic patients, has been used in most HCV models to inform the likelihood of developing advanced liver disease from the cirrhotic health state, i.e. from F4 to DC, from F4 to HCC and from DC to HCC.[134] It is also used for the transition to liver-related mortality from DC and HCC as per most of previous HCV models published in the literature.[23, 26, 111]

The probabilities of undergoing a liver transplant in patients with DC or HCC are based on the Wright et al study [23], which used the transition probability from DC to liver transplant originally based on the Siebert et al [140] study and then assumed the transition probability from HCC to liver transplant to be same as the transition probability from DC to liver transplant.

The model allows for the transition of cirrhotic patients who have achieved SVR to DC and HCC health states; this is supported by the recent evidence from the literature from Cardoso et al. 2010[141] and Bruno et al. 2007[142]. Although the estimates from Cardoso et al study are the most recent, Bruno et al 2007[142] only included patients with cirrhosis. Thus, the estimates from Bruno et al are used for the transition to HCC whereas the Cardoso et al probabilities are used for the transition to DC health state, as the latter was not reported in Bruno et al 2007. The probabilities of dying of liver-related disease following DC and HCC health states were sourced from the aforementioned Fattovich et al study[134]; and the ones following LT and PLT health states from the Bennett et al study. [136]

The re-infection rate was applied from "SVR,F4" to F4 health state and from "SVR,F0-F3" to F0 health state only. The model assumes that patients do not get re-infected from "SVR,F0-

F3" to F1, F2 or F3. The re-infection rate per year was calculated by multiplying the pooled estimate of re-infection among all study participants, as reported in the meta-analysis by Aspinall et al. 2013[143] and the chronicity percentage following re-infection based on Aitken et al. 2008. [144]

Patients achieving SVR are assumed to have a life expectancy equivalent to the general population. [138] This is supported by the Veldt et al 2004 study where the 5-year survival of European sustained virological responders was similar to the overall population, matched for age and sex.[145]

Table 68. Transition probabilities used in the base-case

Annual transition probabilities	Base case value	Source
F0 to F1	0.117	Thein et al, 2008 [139]
F1 to F2	0.085	
F2 to F3	0.120	
F3 to F4	0.116	
F4 to DC	0.039	Fattovich et al, 1997 [134]
F4 to HCC	0.014	
DC to HCC	0.014	
DC to LT	0.022	Siebert et al, 2003 [140]
HCC to LT	0.022	Wright et al, 2006 [23]
DC to LD	0.129	Fattovich et al, 1997 [134]
HCC to LD	0.427	
LT to LD	0.210	Bennett et al, 1997 [136]
PLT to LD	0.057	
F4 SVR to DC	0.012	Cardoso et al, 2010 [141]
F4 SVR to HCC	0.007	Bruno et al, 2007 [142]
F4 SVR to F4	0.014	Aspinall et al, 2013[143]; Aitken et al, 2008[144]
F0-F3 SVR to F0	0.014	

Abbreviations. DC: decompensated cirrhosis; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis; HCC: hepatocellular carcinoma; LD: liver disease; LT: liver transplant (1st year); PLT: post liver transplant (subsequent years); SVR: sustained-virologic response

5.3.3 Probabilities change over time

The transition probabilities used in the base case scenario, sourced from Thein et al[139], do not vary with age; however, Grishchenko et al published data on progression from NC to C based on age.[112] The impact of implementing these transition probabilities was explored in scenario analysis.

The transition probability to death from all causes is age-dependant and sourced from ONS.[138]

5.3.4 Input from clinical experts

The general model structure is consistent with the models used in previous NICE HTA submissions to assess the cost-effectiveness of treatments for CHC.[10-13]

The structure of the model and inputs were validated by two clinical experts during a face to face and a teleconference meeting. Clinical experts were selected on the basis of their knowledge and expertise in treating HCV in England and thus provided recommendations for clinical assumptions within the model: model health states, transition probabilities, AEs associated with therapies, anticipated monitoring requirements of new DAAs, and rates of viral re-infections.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

A number of Phase III clinical trials evaluating the efficacy of EBR/GZR have collected patient reported outcomes as secondary or exploratory endpoints. Generic, disease specific and productivity questionnaires were administered to patients for completion at discrete time points, i.e. at baseline, on treatment and post-treatment period. Table 69 below summarises the PRO instruments and the time points of the measurements for each clinical trial.

Table 69. PRO instruments in phase III clinical trials

Study	PRO instrument	Baseline	On treatment	Post treatment	Treatment discontinuation
C-CO-STAR	SF36v2	Day 1	Week 4, 12, 16 (Deferred treatment arm)	Week 4, 12, 24	Any time point
C-EDGE (Co-infection)	SF-36v2 EQ-5D-5L/EQ-VAS FACIT-Fatigue Scale CLDQ-HCV* WPAI: Hepatitis C	Day 1	Week 4, 12	Week 12, 24	Any time point

Study	PRO instrument	Baseline	On treatment	Post treatment	Treatment discontinuation
C-EDGE TE	SF-36v2 EQ-5D-5L/EQ-VAS FACIT-Fatigue Scale CLDQ-HCV* WPAI: Hepatitis C	Day 1	Week 4, 12, 16	Week 12, 24	Any time point
C-EDGE TN	SF-36v2 EQ-5D-5L/EQ-VAS FACIT-Fatigue Scale CLDQ-HCV* WPAI: Hepatitis C	Day 1	Week 4, 12, 16 (Deferred treatment arm)	Week 4, 12, 24	Any time point
C-SURFER	SF-36v2	Day 1	Week 12, 28 (Deferred treatment arm)	Week 12	Any time point
C-WORTHY	SF-36v2	Day 1	Week 4, 8, 12, 18	Week 12, 24	Any time point
C-EDGE H2H	SF-36v2 EQ-5D-5L FACIT-Fatigue Scale	Day 1	Week 4,12	Week 12, 24	Any time point

Abbreviations. SF36v2, Short Form 36 version 2; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; EQ-VAS, EuroQol Visual Analogue Scale; FACIT, Functional Assessment of Chronic Illness Therapy; CLDQ-HCV, Chronic Liver Disease Questionnaire – Hepatitis C Virus; PRO: Patient-reported outcome; WPAI, Work Productivity and Activity impairment Questionnaire
Note:* Administered only to patients in the U.S

Consistent with the NICE reference case, EQ-5D data were analysed in order to be included in the cost-effectiveness model. Patients co-infected with HIV were excluded from the analysis in order to ensure that any variance in the HRQoL can be attributed solely to EBR/GZR. Consequently, HRQoL data collected from C-EDGE TN, C-EDGE TE and C-EDGE H2H have been pooled across in post-hoc analysis to estimate the impact of EBR/GZR on patients while on treatment and at 12 weeks following end of treatment.

Approximately 37% of all patients that completed EQ-5D-5L questionnaires were European (n=182); however, no UK patients were included. Analyses were performed in data collected from European, as well as, from all subjects enrolled in the trials.

Overall, high completion rates were observed. In relation to the small number of GT4 patients enrolled in these studies (approximately 6% of all subjects), the data may not be considered robust enough, thus GT1 data has been used as proxy. This approach is consistent with the overall approach adopted in the cost-effectiveness analysis, i.e. using GT1 data as a proxy for GT4 in terms of efficacy, discontinuation rates related to AEs and AEs.

The baseline utility values for all patients and European patients are reported in Table 70 and Table 71, respectively. These results are reported irrespective of treatment experience and cirrhosis stage. Overall, European chronic HCV patients in EBR/GZR trials report higher baseline utility values and utility increments.

The pooled analysis also demonstrated that on average GT1 patients that have achieved SVR12 seem to feel better following the successful completion of the treatment course. This is captured in the EQ-5D questionnaires as a utility increment of approximately 0.02 (SE=0.01) and 0.03 (SE=0.01) for all and European chronic HCV patients, respectively. The utility increment was calculated as the difference in the utility between baseline and the follow-up period (i.e. SVR12) only in subjects that have achieved SVR12.

The impact of any AEs on patients' HRQoL was captured in EQ-5D data as part of the change from baseline. To account for any improvement in HRQoL that may have occurred as a result of treatment response, the utility decrement related to AEs has been derived as the difference between baseline and the mean utility values at weak 4 and end-of-treatment. An overall utility decrement of 0% was reported across all patients in the EBR/GZR trials.

Table 70. Summary of utility values of GT1a/GT1b patients in EBR/GZR trials

	All patients			
	N†	Mean, SE (95% CI)	N‡	Change from Baseline, SE (95% CI)
Baseline				
EQ5D-5L Score	497	0.83, 0.01 (0.81, 0.85)		
Week 4				
EQ5D-5L Score	484	0.83, 0.01 (0.82, 0.85)	475	0.00, 0.01 (-0.01, 0.02)
End of Treatment				
EQ5D-5L Score	496	0.84, 0.01 (0.82, 0.86)	487	0.01, 0.01 (-0.01, 0.02)
Mean of Week 4 and End of Treatment				
EQ5D-5L Score	503	0.84, 0.01 (0.82, 0.85)	494	0.00, 0.01 (-0.01, 0.02)
Discontinuation Visit*				
EQ5D-5L Score	0	---, --- (---, ---)	0	---, --- (---, ---)
Follow up visit 12 weeks (only for SVR12 responders)				
EQ5D-5L Score	462	0.85, 0.01 (0.84, 0.87)	453	0.02, 0.01 (0.00, 0.03)

Higher scores indicate better health status.
† N: number of patients with non-missing score.
‡ N: number of patients with non-missing baseline score.
End of Treatment visit was at Week 12 for all subjects
Mean of Week 4 and EOT is arithmetic mean values at subject level. Only subjects whose primary reason for discontinuation was related to adverse events are included.
Only protocols that have subjects with EQ-5D-5L data are included in the table.
* No observed discontinuation related to AE

Table 71. Summary of utility values of GT1a/b patients in EBR/GZR trials

	European patients			
	N†	Mean, SE (95% CI)	N‡	Change from Baseline, SE (95% CI)
Baseline EQ5D-5L Score	182	0.86, 0.01 (0.84, 0.89)		
Week 4 EQ5D-5L Score	178	0.85, 0.01 (0.83, 0.88)	169	-0.01, 0.01 (-0.04, 0.01)
End of Treatment EQ5D-5L Score	189	0.87, 0.01 (0.84, 0.89)	180	0.01, 0.01 (-0.02, 0.03)
Mean of Week 4 and End of Treatment EQ5D-5L Score	190	0.86, 0.01 (0.84, 0.89)	181	-0.00, 0.01 (-0.02, 0.02)
Discontinuation Visit * EQ5D-5L Score	0	---, --- (---, ---)	0	---, --- (---, ---)
Follow up visit 12 weeks (only for SVR12 responders) EQ5D-5L Score	180	0.89, 0.01 (0.87, 0.92)	171	0.03, 0.01 (0.01, 0.05)

Higher scores indicate better health status.
† N: number of patients with non-missing score.
‡ N: number of patients with non-missing baseline score.
End of Treatment visit was at Week 12 for all subjects
Mean of Week 4 and EOT is arithmetic mean values at subject level. Only subjects whose primary reason for discontinuation was related to adverse events are included.
Only protocols that have subjects with EQ-5D-5L data are included in the table.
* No observed discontinuation related to AE

5.4.2 Mapping

HRQL data were collected from EQ-5D-5L questionnaires across the three aforementioned clinical trials. Currently, there are no available EQ-5D-5L value sets derived directly from the UK general population. The EuroQol group has developed the crosswalk based on a response mapping technique that estimated the relationship between responses to the EQ-5D-3L and EQ-5D-5L questionnaires administered to the same patients, and subsequently establishing a link to the 3-level value sets. Thus the UK crosswalk was used to map to EQ-5D-3L utility values. [146]

5.4.3 Systematic searches for relevant HRQoL data

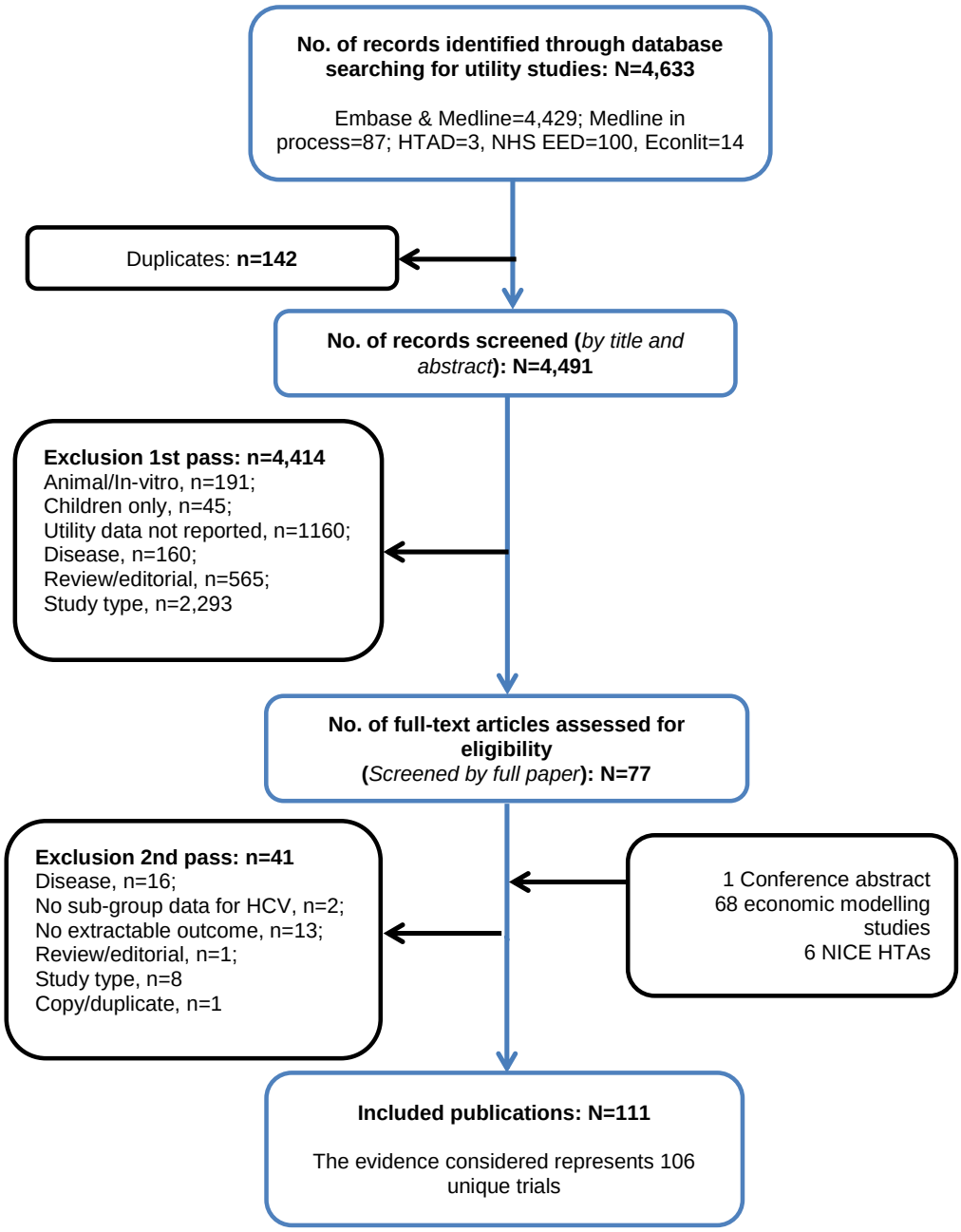
Relevant HRQoL data were identified from the published literature and unpublished data through a SLR search performed between 13 and 19 October 2015, and updated on 20 January 2016, for chronic HCV patients (see appendix 15 for more details). As previously described in section 5.1, the second research question posed in accordance with the decision problem was the assessment of HRQoL (in terms of utilities) associated with chronically infected HCV patients.

A comprehensive literature search relative to this research question was carried out using the different databases presented in section 5.1.1.

All retrieved studies were assessed against the eligibility criteria set out in the final protocol and presented in Appendix 16 where more details of the search strategy are provided. No genotype and geographic restrictions were applied.

From the initial search performed in October 2015, 4,348 references were identified and 285 from the updated search in January 2016. Primary and secondary screenings were conducted by two researchers. Data extraction was performed independently by two reviewers. After removal of 142 duplicates, preliminary screening of abstracts and titles was performed on 4,491 records. After preliminary screening, 77 records were included using the criteria outlined in Appendix 16. The majority of the records (2,293) were excluded on the basis of study type (studies that did not aim to assess utility scores were excluded). Additionally, one study was identified by hand searching and 68 economic modelling studies that reported utility values for HCV patients were also included. Six NICE HTAs were also identified and included. Following review of the full texts, 111 publications were included and relevant data were extracted from 106 unique studies (92 full articles and 14 conference abstracts). The remaining 5 publications sourced their data from the same original publications. The PRISMA flow diagram is presented in Figure 17.

Figure 17. PRISMA flow diagram for HRQoL and utility studies



Abbreviations. HCV, hepatitis C virus; HTA, health technology assessment; HTAD, Health Technology Assessment Database; NHS EED, NHS Economic Evaluation Database; NICE, National Institute for Health and Care excellence; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

5.4.4 Provide details of the studies in which HRQoL was measured

A summary list of published HRQoL and utility studies in the UK is compiled in (Table 72). The non-UK studies (including the ones for which the country is not reported) are provided in appendix 17.

Table 72. Study characteristics and outcomes reported in the identified HRQoL and utility studies identified – UK studies

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
Castelnuovo et al., 2006[147]	UK	Adults with HCV having a documented risk factor of IDU with genotype 1,2,3,4 &5	NR	• PEG-IFN-2a+RBV	• EQ-5D	Mild, Moderate, Severe, cirrhotic, HCC, DCC, LT & Post LT	• NR	**Mild:** • Non-symptomatic: 0.79 • Symptomatic: 0.75 • During treatment: 0.65 • Sustained response: 0.82 • Non-responders: 0.76 **Moderate:** • Non-symptomatic: 0.68 • Symptomatic: 0.64 • During treatment: 0.55 • Sustained response: 0.72 • Non-responders: 0.65 **Severe:** • Non-symptomatic: 0.60 • Symptomatic: 0.56 • During treatment: 0.50 • Sustained response: 0.66 • Non responders: 0.61 **Cirrhotic:** • Non-symptomatic: 0.55 • Symptomatic: 0.51 • During treatment: 0.46 • Sustained response: 0.61 • Non responders: 0.55 **HCC:**

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
								• Non-symptomatic: 0.45 • Symptomatic: 0.41 **Decompensated liver disease:** • Non-symptomatic & symptomatic: 0.45 **Waiting list for LT:** • Non-symptomatic: 0.45 **LT:** • Non-symptomatic: 0.45 **Post LT, decompensated:** • Non-symptomatic: 0.45 **Post LT, healthy:** • Non-symptomatic: 0.67
Grieve et al., 2006[110] **	UK	Patients with mild CHC	196	• IFN α-2b+RBV • PEG-IFN α-2b+RBV • NT	• EQ-5D	Mild disease, Treatment for mild disease, Post-SVR, Moderate disease, Cirrhosis, DCC, HCC,LT	**Mean health state utility (SD):** • Mild disease (n=185): 0.77 (0.22)	**Mean health state utility (SD):** • Treatment for mild disease (n=80): 0.66 (0.32) • Post-SVR (n=24): 0.82 (0.21) • Moderate disease (n=71): 0.66 (0.25) • Cirrhosis (n=40): 0.55 (0.34) • DCC (n=64): 0.45 (0.24) • HCC (n=64): 0.45 (0.24) • LT (n=64): 0.45 (0.24)
Wright et al., 2006[23]	UK	Adult patients with mild chronic HCV with genotype 1, non-1	A total of 130 patients completed a follow-up EQ-5D questionnaire at 24 or 48 weeks	• PEG-IFN-2b (48 weeks) • NT	• EQ-5D	Mild disease, Moderate disease, Cirrhosis, HCC, Treatment for mild disease, Treatment for moderate disease, DCC, Post-LT, Mild & moderate disease SVR	Mean (SD) HRQoL (EQ-5D) for treatment versus control groups at follow-up (24/48 weeks post-treatment **Follow-up:** • Control (n=61): 0.76 (0.22) • Treatment (n=69): 0.77 (0.30) • Difference in means (95% CI): 0.02 (–0.08 to 0.10) **Baseline:** • Control (n=61): 0.79 (0.19) • Treatment (n=69): 0.76 (0.19)	Mean (SD) HRQoL (EQ-5D) for treatment versus control groups at follow-up (24/48 weeks post-treatment) **Follow-up:** • Control (n=61): 0.76 (0.22) • Treatment (n=69): 0.77 (0.30) • Difference in means (95% CI): 0.02 (–0.08 to 0.10) Mean (SD) HRQoL at follow-up for control group, versus treatment non-SVRs and treatment SVRs **Follow-up:** • Control (n=61): 0.76 (0.22)

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
			post-treatment (or control) (Treatment group: 69 Control: 61)				• Difference in means (95% CI): –0.03 (–0.10 to 0.06) Mean (SD) HRQoL at follow up for control group, versus treatment non-SVRs and treatment SVRs **Baseline:** • Control (n=61): 0.79 (0.19) • Treatment Non-SVR (n=45): 0.75 (0.30) • Treatment SVR (n=24): 0.80 (0.22) Mean (SD) HRQoL (EQ-5D) results for treatment versus control groups at 12/24 weeks post-randomisation **Baseline:** • Control (n=64): 0.75 (0.23) • Treatment (n=80): 0.79 (0.26) • Difference in means (95% CI): 0.03 (–0.04 to 0.11)	• Treatment Non-SVR (n=45): 0.75 (0.34) • Treatment SVR (n=24): 0.82 (0.21) Mean (SD) HRQoL (EQ-5D) results for treatment versus control groups at 12/24 weeks post-randomisation **12 or 24 week change:** • Control (n=64): 0.79 (0.26) • Treatment (n=80): 0.66 (0.32) • Difference in means (95% CI): –0.09 (–0.20 to 0.1) Mean (SD) HRQoL for each disease stage • Mild disease: 0.77 (0.22) • Moderate disease: 0.66 (0.25) • Cirrhotic: 0.55 (0.34) • HCC: 0.45 • Treatment for mild disease: 0.65 • Treatment for moderate disease: 0.55 • DCC: 0.45 • Post-liver transplantation: 0.67 • **SVR after mild disease:** 0.82 • **SVR after moderate disease:** 0.72

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
Shepherd et al., 2007[111]**	UK	Adults with mild chronic HCV with genotype 1,2 & 3	NR	• PEG-IFN-2a/2b+RBV (48 weeks) • IFN-2a/2b+RBV(48 weeks) • BSC	• EQ-5D	Mild HCV, Moderate HCV, CC, HCC, DCC, LT	• NR	• Mild SVR: 0.82 • Moderate SVR: 0.72 • Mild CHC: 0.77 • Treatment for mild CHC & moderate CHC: 0.66 • Treatment for moderate CHC & cirrhosis: 0.5 • DCC, HCC & LT: 0.45
Sutton et al., 2008[148]	UK (England and wales)	HCV Patients with genotype 2/3 and other genotype	• NR	• **Genotype 2 and 3:** PEG-IFN+RBV (24 weeks) • **Other Genotype:** PEG-IFN +RBV (48 weeks)	• NR	Mild, Moderate, Cirrhotic, HCC, DCC, LT, Liver related death	• NR	**Utility (mean, SE):** **Non-symptomatic:** **Undiagnosed:** • Mild: 0.79 (0.024) • Moderate: 0.64 (0.03) • Cirrhotic: 0.55 (0.054) • HCC: 0.45 (0.056) • DCC: 0.45 (0.056) • Post-LT: 0.67 (0.067) **Symptomatic:** **Diagnosed:** • Mild: 0.75 (0.024) • Moderate: 0.60 (0.03) • Cirrhotic: 0.51 (0.054) **During treatment:** • Mild: 0.65 (0.002) • Moderate: 0.525 (0.003) • Cirrhotic: 0.46 (0.005) **Sustained response:** • Mild: 0.82 (0.005) • Moderate: 0.69 (0.0065) • Cirrhotic: 0.61 (0.006) **Non-responder:** • Mild: 0.76 (0.003) • Moderate: 0.63 (0.0051) • Cirrhotic: 0.55 (0.0038)

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
Grishchenko et al., 2009[112]**	UK	TN, CHC with genotype 1 & non-1	315	• PEG-IFN+RBV • NT	• EQ-5D	SVR, mild disease, moderate disease, cirrhosis, HCC, DCC, LT, post-LT, liver related death	• NR	**HRQL (absolute values) of 50 years of age at treatment:** • Mild stage: 0.77 • During treatment for mild HCV: 0.66 • SVR following treatment for mild HCV: 0.82 • Moderate stage: 0.66 • During treatment for moderate HCV: 0.55 • SVR following treatment for moderate HCV: 0.71 • Cirrhosis: 0.55 • During treatment for patients with cirrhosis: 0.44 • SVR following treatment for cirrhosis: 0.60 • DCC, HCC: 0.45
Hartwell et al., 2011[26]**	UK	Adults with chronic HCV with genotype 1, 2, 3 & 4	NR	• PEG-IFN-2a/2b+RBV • PEG-IFN 2a/2b • BSC • PEG-IFN-2a+RBV	• EQ-5D	SVR, Mild HCV, Moderate HCV, CC, HCC, DCC, LT & Death	• NR	• Mild SVR: 0.82 • Moderate SVR: 0.72 • Mild CHC: 0.77 • Treatment for mild HCV & moderate HCV: 0.66 • Treatment for moderate HCV & cirrhosis: 0.5 • DCC, HCC & LT: 0.45 • Post LT: 0.67
NICE, 2011a [TA253] [39]	UK	TN & TE adults with chronic HCV with genotype 1	• NR	• BOC+PEG-IFN+RBV • PEG-IFN+RBV	• EQ-5D	F0-4, SVR F0, SVR F1, SVR F2, SVR F3, F4 CC/SVR, DCC,HCC, LT (first year) , Liver related death, Post LT	• NR	**Health state QoL weights:** • Mild HCV (F0 & F1): 0.77 • Moderate HCV(F2 & F3): 0.66 • CC: 0.55 • SVR (depends on the initial state before treatment SVR 0 &1): 0.82 • SVR (depends on the initial state before treatment SVR 2&3): 0.72

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
								• SVR (depends on the initial state before treatment SVR 4): 0.60 • DCC, DCC subsequent years, HCC, HCC subsequent years & LT (first year): 0.45 • LT(subsequent years): 0.67 **QoL of treated patients:** • F0-F1: 0.66 • F2-F3: 0.55 • F4: 0.44 • Other major side effects: 0.88 • Anaemia: 0.89
NICE, 2011b [TA252] [38]	UK	TN & TE adults with chronic HCV with genotype 1	• NR	• TVR+PEG-IFN+RBV • PEG-IFN+RBV	• EQ-5D	SVR, Mild HCV, Moderate HCV, CC, HCC, DCC, LT	• Mild: 0.77 • Moderate: 0.66 • CC: 0.55	**Following SVR** • Mild: 0.82 • Moderate: 0.72 • CC: 0.61 **Following No SVR:** • Mild: 0.77 • Moderate: 0.66 • CC: 0.55 • DCC: 0.45 • HCC: 0.45 • LT: 0.45 • Post LT: 0.67 **TN:** **Treated with TVR/PEG-IFN+RBV:** • Mild: 0.67 • Moderate: 0.56 • CC: 0.45 **Treated with PEG-IFN+RBV:** • Mild: 0.66 • Moderate: 0.55 • CC: 0.44 **TE:**

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
								Treated with TVR/PEG-IFN+RBV: • Mild: 0.62 • Moderate: 0.51 • CC: 0.40 **Treated with PEG-IFN+RBV:** • Mild: 0.64 • Moderate: 0.53 • CC: 0.42
Martin et al., 2012[149]**	UK	• HCV with IDUs and ex/non-IDUs • HCV patients with50% genotype 1 and50% genotype 2/3	• Endemic infection population numbers in each disease category (IDU and ex/non-IDU) given a total population of 1,000 IDUs	• PEG-IFN-a+RBV (AVT treatment for IDUs as compared with treating ex/non-IDUs or NT)	• EQ-5D Health utilities (measured in QALYs)	Mild, moderate, cirrhosis, DCC, HCC, LT, post-LT, and liver-related death	• NR	**Health Utility Values: Mean Yearly Value [95% Interval]:** • Uninfected: Values for Ex/non-IDU, and IDU were : 0.85 • Mild HCV*: 0.77 [0.74-0.80] • Moderate HCV*: 0.66 [0.60-0.72] • Cirrhosis*: 0.55 [0.44-0.65] • DCC*: 0.45 [0.39-0.51] • HCC*: 0.45 [0.39-0.51] • LT*: 0.45 [0.39-0.51] • Post-transplant*: 0.67 [0.53-0.79] **On treatment:** • Mild*: 0.66 [0.59-0.73] • Moderate*: 0.55 [0.44-0.65] **SVR:** • Mild*: 0.82 [0.73-0.90] • Moderate*: 0.72 [0.62-0.81] *Value for both IDU and ex/non-IDU
McDonald et al., 2013[150]	Scotland	Chronic HCV	2,898	• NR	• EQ-5D	• NR	• NR	**Median (IQR):** • Non chronic HCV: 0.73 (0.35–0.84)

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
		patients						• Chronic/unaware: 0.73 (0.31–1.0) • Chronic/aware: 0.66 (0.21–0.85)
McEwan et al.2013[121]**	UK	CHC genotype1 patients	• NR	• PEG-IFN-2a+RBV (48 weeks) • RGT	• EQ-5D	SVR, chronic HCV, fibrosis stage F4, CC, DC, HCC and LT	Baseline: 0.85	• On treatment (F0, F1): 0.66 • On treatment (F2, F3): 0.55 • Sustained virological response: 0.82 • Chronic HCV (F0 State): 0.77 • Chronic HCV (F1 State): 0.77 • Chronic HCV (F2 State): 0.66 • Chronic HCV (F3 State): 0.66 • Chronic HCV (F4 State): 0.55 • DC: 0.45 • HCC: 0.45 • LT (Year 1): 0.45 • LT (Year 2+): 0.45
Cure et al., 2014a[122]**	UK	TN, CHC adults with genotype 1	NR	• PEG-IFN+RBV • TVR+PEG-IFN+RBV • BOC+PEG-IFN+RBV	• EQ-5D	Mild fibrosis, moderate fibrosis, CC, DCC, LT, post-LT, HCC, SVR, death	• NR	**Base case utilities:** **Utilities for mild fibrosis:** • Without treatment: 0.77 • PEG-IFN+RBV: 0.675 • TVR+PEG-IFN+RBV: 0.682 • BOC+PEG-IFN+RBV: 0.682 • SVR following treatment: 0.82 **Utilities for moderate fibrosis:** • Without treatment: 0.66 • PEG-IFN+RBV: 0.579 • TVR+PEG-IFN+RBV: 0.585 • BOC+PEG-IFN+RBV: 0.585 • SVR following treatment: 0.72 **Utilities for cirrhosis:** • Without treatment: 0.55 • PEG-IFN+RBV: 0.482 • TVR+PEG-IFN+RBV: 0.487 • BOC+PEG-IFN+RBV: 0.487 • SVR following treatment: 0.61 **Utilities for DCC, HCC and LT:**

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
								• Advanced disease stages: 0.45 **Utilities for Post-LT:** • Advanced disease stages: 0.67
Matza et al., 2014[151]	UK	HCV patients	182	• NR	• TTO	• Health states differing by treatment regimen and AEs (A-N)*	• Not Required	**Hepatitis C health states utility: Mean (SD)** **Health states (1; 10-year time horizon):** • A*: 0.81 (0.29); 0.80 (0.30) • B*: 0.81 (0.29); 0.80 (0.30) • C*: 0.80 (0.29); 0.79 (0.30) • D*: 0.79 (0.29); 0.79 (0.30) • E*: 0.77 (0.30); 0.77 (0.30) • F*: 0.76 (0.32); 0.75 (0.31) • G*: 0.72 (0.35); 0.71 (0.35) • H*: 0.72 (0.33); 0.71 (0.35) • I*: 0.65 (0.38); 0.65 (0.36) • J*: 0.47 (0.41); 0.45 (0.42) • K*: 0.57 (0.39); 0.56 (0.39) • L*: 0.66 (0.37); 0.65 (0.40) • M*: 0.34 (0.47); 0.30 (0.50) • N*: 0.33 (0.48); 0.31 (0.48)
NICE, 2014a [TA364] [12]	UK	Adults with CHC with genotype 1, 3 & 4	182	• PEG-IFN+ RBV • NT • SMV+PEG-IFN+RBV • TVR+PEG-IFN+RBV • SOF+PEG-IFN+RBV • BOC+PEG-IFN+RBV • DCV+SOF • SMV+SOF • SOF+RBV	• TTO	SVR, F0-4, DCC, HCC, LT & Death	NR	**Mean F0-F4 fibrosis stages** • F0 & F1: 0.77 • F2 & F3: 0.66 • F4: 0.55 **Mean SVR** • SVR from F0-F1: 0.82 • SVR from F2-F4: 0.72 **Mean complications** • DCC, HCC & LT(initial year): 0.45 • LT(subsequent years): 0.67 **Mean treatment related disutility** • PEG-IFN+ RBV (TN): 0.109 • PEG-IFN+ RBV (TE): 0.126 • TVR+PEG-IFN+RBV: 0.102

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
				• DCV+PEG-IFN+RBV				• BOC+PEG-IFN+RBV: 0.0671 • SMV+PEG-IFN+RBV: 0.798 • SMV+SOF: 0.798 • SOF+PEG-IFN+RBV: 0.148 • DCV+SOF: 0.035 • DCV+PEG-IFN+RBV: 0.137 • DCV+SOF+PEG-IFN+RBV: 0.059 • SOF+RBV: 0.048
NICE, 2014b [TA363] [11]	UK	• Genotype 1 TN • Genotype 4 TN • Genotype 1 & 4 TE • Genotype 3 TN and TE (unsuitable for IFN therapy), HCV patients	NR	• LDV+SOF • SOF+PEG-IFN-a+RBV • SMV+PEG-IFN-2a+RBV • PEG-IFN-2a+RBV • TVR+PEG-IFN-2a+RBV • BOC+PEG-IFN-2a+RBV • NT • SMV+SOF	• EQ-5D (US EQ-5D tariff)	SVR (utility increment), After treatment at non-cirrhotic stage, After treatment at cirrhotic stage, Baseline – non-cirrhotic, Baseline – CC, DCC, HCC, LT, Post-LT	**Utility values of Health states**: • Baseline – non-cirrhotic: 0.75 • Baseline – CC: 0.55	**Utility values of Health states**: • SVR (utility increment): 0.04 • After treatment at non-cirrhotic stage: 0.79 • After treatment at cirrhotic stage: 0.59 • DCC: 0.45 • HCC: 0.45 • LT: 0.45 • Post-LT: 0.67
NICE, 2014c [TA365] [13]	UK	• TN & TE adults with chronic HCV with genotype 1 & 4	NR	• OMV+PRV+RTV+DSV • OMV+PRV+RTV • BOC+PEG-IFN+RBV • TVR+PEG-IFN+RBV • SOF+PEG-IFN+RBV	• EQ-5D	Mild HCV, moderate HCV, CC, HCC, DCC, LT and Post LT	NR	**Health state utility values:** • Mild HCV: 0.77 • Moderate HCV: 0.66 • CC: 0.55 • Recovered (no HCV, history of mild fibrosis): 0.82 • Recovered (no HCV, history of moderate fibrosis): 0.71 • Recovered (no HCV, history of CC): 0.60

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
				• PEG-IFN+RBV • NT				• DCC: 0.45 • HCC: 0.45 • LT: 0.45 • Post-LT: 0.67
NICE, 2014d [TA330] [10]	UK	• TN patients with HCV genotype 1 infection • TN and TE patients with HCV genotype 2 & genotype 3 infection • TN genotype 4, 5 or 6 HCV Patients	NR	• SOF+PEG-IFN-2a+RBV • NT • PEG-IFN-2a+RBV • TVR+PEG-IFN-2a+RBV • BOC+PEG-IFN-2b+RBV • SOF+RBV • NT	• EQ-5D	Baseline – non-cirrhotic, Baseline – compensated cirrhosis, SVR (utility increment), After treatment at non-cirrhotic stage, After treatment at cirrhotic stage, DCC, HCC, LT, Post-LT	**Utility values used by the manufacturer:** • Baseline-non-cirrhotic: 0.74 • Baseline-compensated cirrhosis: 0.55	**Utility values used by the manufacturer:** • Sustained virological response (utility increment): 0.05 • After treatment at non-cirrhotic stage: 0.79 • After treatment at cirrhotic stage: 0.60 • DCC: 0.45 • HCC: 0.45 • LT: 0.45 • Post-LT: 0.67
McEwan et al., 2015a[129]**	UK	Genotype1 HCV patients	NR	• DCV+SOF • TVR+PEG-IFN+RBV • NT	• NR	No fibrosis (F0), Portal fibrosis with no septa (F1), Portal fibrosis with few septa (F2), Portal fibrosis with many septa (F3), CC (F4), DC, HCC, LT, Post-SVR	• NR	**Health utility of disease state:** • F0: 0.77 • F1: 0.77 • F2: 0.66 • F3: 0.66 • F4: 0.55 • DC: 0.45 • HCC: 0.45 • LT (Year 1): 0.45 • LT (Year 2+): 0.67 • Post-SVR (F0-F1): 0.82 • Post SVR (F2-F3): 0.72 • Post-SVR (F4): 0.72

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
Pol et al., 2015[152]	France, UK and Germany	Patients with HCV	831	NR	• EQ-5D	• NR	• NR	**Mean (SE) utility values:** • F0-F1 (n=239): 0.82 (0.02) • F2 (n=246): 0.78 (0.02); • F3-F4 (n=101): 0.67 (0.03) • DCC/HCC (n=25): 0.51 (0.07) **LT:** • Initial year (n=5): 0.46 (0.10) • Subsequent years (n=10): 0.80 (0.08) • Unclassified (n=205): 0.79 (0.02) SVR: • F0-F1 (n=35): 0.95 (0.01) • F2-F3-F4 (n=36): 0.85 (0.02)
Westerhout et al., 2015[131]**	UK	CHC patients with genotype 1	NR	LDV ± RBV+SOF SOF+SMV	• NR	SVR F0/F2: Y1, SVR F3: Y1, SVR F4: Y1-5, F0/F2, F3, F4, DCC, HCC, LT, Post-LT, On-treatment disutility	• NR	**Health states utility:** • SVR F0/F2: Y1: 0.82 • SVR F3: Y1: 0.71 • SVR F4: Y1-5: 0.60 • F0/F2: 0.77 • F3: 0.66 • F4: 0.55 • DCC: 0.45 • HCC: 0.45 • LT: 0.45 • Post-LT: 0.67 • On-treatment disutility: -0.03

Abbreviations. EQindex, euroQol index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HLQ, health and labour questionnaire; HQLQv2, hepatitis quality of life questionnaire version 2; HTLV, human T-lymphotropic virus type; HPW, health preference weights; HUI 2, health utilities index mark 2; HUI 3, health utilities index mark 3; IDUs, injecting drug users; IE, interferon eligible; IFN, interferon; LDSI, liver disease symptom index; IQR, inter quartile range; LT, liver transplantation; NR, not reported; NT, no treatment; OLT, orthotopic liver transplantation; PBC, primary biliary cirrhosis; PEG, polyethylene glycol; PI, protease inhibitor; RBV, ribavirin; SD, standard deviation; SE, standard error; SF-6D, short form-6 domain; SF-12v2, short form-12 version 2; SF-36, short form-36; SG, standard gamble; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response; TN, treatment naïve; TE, treatment experienced; TTO, time-trade-off; TVR, telaprevir; VAS, visual analogue scale

Notes:

*HCV health states (Health states differing by treatment regimen): A. All-oral regimen (1 tablet per day); B. All-oral regimen (2 tablets per day); C. All-oral regimen (3 tablets per day); D. All-oral regimen (7 tablets per day); E. Oral treatment (7 tablets per day)+weekly injection; F. Oral treatment (12 tablets per day)+weekly injection; G. Oral treatment (12 tablets per day taken with fatty food)+weekly injection; H. Oral treatment (18 tablets per day)+weekly injection Health states differing by adverse events; I. Health state E+mild aneamia J. Health state E+severe aneamia; K. Health state E+flu-like syndrome; L. Health state E+mild rash; M. Health state E+severe rash; N. Health state E+depression

***This publication refers to the same original publication Wright et al 2006 [23]

5.4.5 Key differences between the values derived from the literature search and those reported in or mapped from the clinical trials

Overall, the baseline utility values reported in the EBR/GZR trials were higher than the values reported by Wright et al [23] in chronic HCV UK patients, which have consistently been used in the majority of NICE submissions [11-13], and published cost-effectiveness analysis models identified in section 5.4.5 above[26, 110-112, 121, 122, 129, 131, 149]. Wright et al reported specific utility values for mild (F0-F1), moderate (F2-F3) and severe (F4) disease that reflect the impact on the patient's HRQoL as the disease progresses in severity.

An average utility increment of 0.05 was reported by Wright et al, which reflected the impact on HRQoL on HCV patients achieving SVR. [23] Although this value is slightly higher than the values estimated from EBR/GZR clinical trials; it is potentially more reflective of successful treatment in a UK patient population as no UK patients were enrolled in the EBR/GZR trials collecting EQ-5D data. For the reasons highlighted above and in order to be consistent with previous submissions, the utility values reported in the study by Wright et al will be used in the base case and utility increment values from EBR/GZR trials will only be used in scenario analysis.

5.4.6 Describe how adverse reactions affect HRQoL

The impact of any AEs during treatment is captured by monitoring the HRQoL of the patient across the treatment course. This is done via the application of a treatment-specific utility decrement to baseline utility while on treatment. Where evidence is available, the utility decrement related to an AE also varies for treatment naïve and experienced patients. The impact of EBR/GZR AEs has been captured in the EQ-5D data collected in the trials (see section 5.4.1) while the utility decrements associated with the comparators' AEs were derived from the literature. In cases where comparators' data were not available, the disutility values of EBR/GZR treatment were applied to comparator products as a conservative approach. Generally, interferon based regimens are associated with decreased HRQoL primarily related to AEs such as fatigue, anaemia, nausea and thrombocytopenia. Treatments administered in combination with PR such as SOF+PR have reported similar AEs to the ones reported on PR therapy alone. Table 73 below summarises the utility decrements for EBR/GZR and comparator regimens.

Table 73. On-treatment utility decrements for patients with GT1 and 4

Treatment	TN mean (SE)	TE mean (SE)	Sources
EBR/GZR	0.000 (0.01)	0.000 (0.01)	Data on file
No Treatment	0.000 (0.000)	0.000 (0.000)	
PR	-0.109 (-0.10)	-0.126 (-0.018)	TA252 (National Institute for Health and Care Excellence (NICE), 2012) [38]

Treatment	TN mean (SE)	TE mean (SE)	Sources
SOF	-0.145 (-0.015)	-0.145 (-0.015)	TA363 (National Institute for Health and Care Excellence (NICE), 2015c). NEUTRINO trial –Mapped SF-6D[11]
SMV	-0.081 (-0.008)	-0.119 (-0.012)	TA331 (National Institute for Health and Care Excellence (NICE), 2015b) [40]
3D/2D	0.000 (0.01)	0.000 (0.01)	Assumed to be same as EBR/GZR
LDV/SOF	0.000 (0.000)	0.000 (0.000)	TA363 (National Institute for Health and Care Excellence (NICE), 2015c) [11]
DCV+SOF	-0.035 (-0.004)	-0.035 (-0.004)	TA364 (National Institute for Health and Care Excellence (NICE), 2015d) [12]
DCV+PR	-0.137 (-0.014)	-0.137 (-0.014)	

Abbreviations. 3D/2D, ombitasvir/paritaprevir/ritonavir ± dasabuvir; DCV, daclatasvir-based treatment; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PR, peginterferon+ribavirin; SE, standard error; SMV, simeprevir; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naïve

5.4.7 Definition of the health states in terms of HRQoL in the cost-effectiveness analysis.

Each health state in the model is associated with a health utility value. It is assumed that the F0-F1 states are categorised as mild disease, F2-F3 as moderate disease and F4 as severe disease. Within these categories, the utility values assigned are identical. However, the HRQoL utilities decrease as patients progress to more severe health states i.e. from mild fibrosis to compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplant. An increase in HRQoL is observed when patients achieve SVR or at the year following a successful liver transplant.

5.4.8 Clarification on whether HRQoL is assumed to be constant over time in the cost-effectiveness analysis

Health states within the model are assigned a constant utility value, with more advanced health states assigned lower utility values. Utility decrements associated with AEs while on-treatment have been assigned based on published literature for the comparator regimens and analysis of post-hoc trial data for EBR/GZR (see section 5.4.1). Variances in these utility and disutility values are explored as part of the sensitivity analysis.

Additionally, to reflect the decrease in HRQoL observed in the general population as they aged, the baseline utility values have been adjusted using the methodology reported from Kind et al. 1998 study. [153]

5.4.9 Description of whether the baseline HRQoL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states

Health state utility values within the model have been adjusted to be age-dependent. Please see the section 5.4.10 for the details.

5.4.10 Description of how and why health state utility values used in the cost-effectiveness analysis have been adjusted, including the methodologies used

The average utility values of the UK population are age and sex dependant and are derived from the study by Kind et al. 1999, see Table 74. [153] The average annual utility decrement between the starting age (i.e. 40 and 45 for TN and TE patients, respectively) and 75 years of age has been calculated (-0.0049 for TN and -0.0035 for TE) and was further increased in a linear fashion with aging. The utility weights for health states used in our model were calculated by subtracting those age-dependent utility decrement from the utility values assigned to each health state. The age-dependent utility decrements were assumed to remain constant after the age of 75.

Table 74. Average utility of UK population by age group[153]

	Mean		SE		Weighted sum	
	Male	Female	Male	Female	Mean	SE
Under 25	0.94	0.94	1.36	1.59	0.940	1.43
25-34	0.93	0.93	2.91	3.09	0.930	2.96
35-44	0.91	0.91	2.72	2.62	0.910	2.69
45-54	0.84	0.85	4.01	3.76	0.843	3.94
55-64	0.78	0.81	3.92	4.41	0.789	4.07
65-74	0.78	0.78	4.23	4.03	0.780	4.17
75+	0.75	0.71	2.91	3.88	0.738	3.20

Abbreviations. SE, standard error

5.4.11 Identification of any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis

No health effects were excluded from the cost-effectiveness analysis. Alternative utility increment values were used as scenario analysis to reflect the uncertainty around the selected inputs.

5.4.12 Summary of utility values chosen for the cost-effectiveness analysis, referencing values obtained in sections 5.4.1–5.4.6.

The base-case health state utility values are derived from the published literature, specifically Wright et al. 2006[23] (see Table 75), which was consistently referenced in previous submissions. These values showed that as the disease progresses from mild fibrosis to compensated cirrhosis, health utility (based on the EQ-5D) declines from 0.77 to 0.55. More advanced liver disease is associated with even lower utilities, e.g. 0.45 for DCC, HCC and liver transplant. These utilities are considered appropriate to the NICE reference case[137] for measuring and valuing health benefits, in that the quality of life measurements were undertaken using the EQ-5D instrument. These were originally obtained from three

different studies; a UK Mild HCV RCT trial, an observational study of moderate and more severe HCV patients conducted alongside the trial, and a large UK transplantation study.[154]

These values are tested in the deterministic sensitivity analysis (DSA), by varying individually the base case health state utilities. Achieving SVR, captured in the model by the SVR health states, has shown to positively improve baseline HRQoL. Based on Wright et al. 2006[23], achieving SVR from mild fibrosis, moderate fibrosis or compensated cirrhosis is associated with a 0.05 increase in health utility. This assumption is tested based on the SVR-related utility increments of European HCV patients identified in the EBR/GZR clinical trials in a scenario analysis.

Table 75. Summary of utility values for cost-effectiveness analysis

Health State	Mean	SE	Reference in submission (section and page number)	Justification
F0	0.77	0.02	Section 5.4.4, Table 72, page 207	Utility values from published data in line with NICE reference case[137]
F1	0.77	0.02		
F2	0.66	0.03		
F3	0.66	0.03		
F4	0.55	0.05		
DCC	0.45	0.045		
HCC	0.45	0.045		
LT	0.45	0.045		
PLT	0.67	0.067		
Utility increment	0.05	0.005		
SVR, F0	0.82	0.04		
SVR, F1	0.82	0.04		
SVR, F2	0.71	0.05		
SVR, F3	0.71	0.05		
SVR, F4	0.49	0.05		

Abbreviations. DC, decompensated cirrhosis; F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis; HCC, hepatocellular carcinoma; LD, liver-related death; LT, liver transplant (first year); PLT, liver transplant (subsequent years); SE, standard error; SVR; sustained virological response

5.4.13 Details if clinical experts assessed the applicability of the health state utility values available or approximated any of values

The applicability of the selected health state utility values was not assessed by clinical experts as these values were in line with those in the published literature and overall consistent with the NICE reference case.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Parameters used in the cost effectiveness analysis

A summary of the variables used in the cost estimation is presented in Appendix 18.

The type of costs included in the model aimed to reflect the clinical management of patients with CHC: treatment costs (including drug), monitoring and follow-up of patients, management of complication related to AEs.

5.5.2 Resource identification, measurement and valuation studies

A SLR was performed to identify cost and resource use associated with the treatment of HCV population. The search strategy, inclusion/exclusion criteria and results table are respectively provided in Appendix 19, Appendix 20 and Appendix 21. From the first search performed in October 2015, 4,999 references were initially identified and 376 from the updated search in January 2016. Primary and secondary screenings were conducted by two researchers. Data extraction was performed by a single reviewer. After removal of 150 duplicates, preliminary screening of abstracts and titles was performed on 5,225 records. After preliminary screening, 68 records were included using the criteria outlined in Appendix 20. The majority of the records were excluded on the basis of study type (2,683), followed by review/editorial (1,206). Following review of the full texts, 38 publications (including one identified by the updated search in January 2016) were included and relevant data were extracted from 35 unique studies (three publications sourced their data from the same original publication).

5.5.3 Use of NHS reference costs or payment-by-results (PbR) tariffs

The management of chronic HCV is not included in the PbR tariff. The NHS reference costs are used for the unit costs of managing patients while on treatment. [155] This is a conservative approach as the NHS reference costs reflect the real cost to the service while the PbR tariffs reflect the service reimbursed. In addition, there is a greater level of granularity with reference costs, which allows the implementation of a more precise and detailed micro-costing approach. This approach has been adopted in previous NICE assessments (TA330; TA331; TA363; TA364; TA365).[10-13, 40]

5.5.4 Input from clinical experts

Please see section 5.3.4.

5.5.5 Intervention and comparators' costs and resource use

Drug costs

The comparators' list prices were sourced from the Monthly Index of Medical Specialities (MIMS, accessed on 30th March 2016) except for RBV therapy where the drugs and pharmaceutical electronic market information (eMit, downloaded on 30th March 2016) database was searched (see Table 76). [16, 156] The SPCs were used to assess the dose

required. Unit drug costs were presented per week. The doses of both PEG and RBV vary by weight; an average body weight of 79kg was used based on the Hartwell et al study.[26] When more than one drug was available (i.e. Pegasys® and Viraferon® for peginterferon; and Rebetol® and Copegus® for ribavirin), market share estimates were used to calculate a weighted average price, based on the IMS HPA data (Dec 2015) [157]. When various prices per pack were available, the weekly drug cost was calculated based on the cheapest agent. The total treatment cost accounts for the drug costs and the treatment duration as defined in section 5.3.1.

Table 76. Treatment unit costs

Therapy		Drug	Cost per pack (£)	Unit Dose	Quantity per pack	Recommended dose per day	Market share	Weekly cost	Source
EBR/GZR		Zepatier®	£12,166.67	100/50 mg	28	100/50	N/A	£3,041.67	MSD
PEG	Overall	Weighted sum						£130.79	Weighted average
	PEG-2a	Pegasys®	£76.51	90 mcg	1	25.71mcg	80.7%	£153.02	MIMS March 2016[16]
			£107.76	135 mcg	1			£143.68	
			£497.60	180 mcg	4			£124.40	
	PEG-2b	Viraferon Peg®	£66.46	50 mcg	1	16.93mcg	19.3%	£157.51	
			£106.34	80 mcg	1			£157.52	
			£132.92	100 mcg	1			£157.51	
			£159.51	120 mcg	1			£157.52	
			£199.38	150 mcg	1			£157.51	
RBV		Weighted sum						£16.22	Weighted average
		Copegus ®	£92.50	200mg	42	1161.4mcg	70.1%	£27.55	eMit[156]
			£246.65	200mg	112			£15.31	
			£369.98	200mg	168			£16.68	
		Rebetol®	£160.69	200mg	84	1200mcg	29.3%	£22.34	
			£267.81	200mg	140			£18.35	
			£321.38	200mg	168			£22.05	
SOF		Sovaldi®	£11,660.98	400 mg	28	400mcg	N/A	£2,915.25	MIMS March 2016[16]
SMV		Olysio®	£1,866.50	150 mg	7	150mcg	N/A	£1,866.50	
3D	Overall	Sum of Viekirax® and Exviera®						£2,916.67	
	2D	Viekirax®	£10,733.33	12.5/75/50 mg	56	25/150/100mcg	N/A	£2,683.33	
	Dasabuvir	Exviera®	£933.33	250 mg	56	500mcg	N/A	£233.33	
2D		Viekirax®	£10,733.33	12.5/75/50 mg	56	25/150/100mcg	N/A	£2,683.33	
LDV/SOF		Harvoni®	£12,993.33	90/400 mg	28	90/400mcg	N/A	£3,248.33	
DCV		Daklinza®	£8,172.61	60 mg	28	60mcg	N/A	£2,043.15	

Abbreviations. 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PEG: peginterferon; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Monitoring costs

The monitoring costs refer to the costs incurred whilst patients are being treated with EBR/GZR or the comparator treatments. These costs are presented Table 77. The monitoring costs per regimen vary according to the treatment duration. The on-treatment monitoring costs for PR, SOF, SMV and LDV/SOF are derived from the previous appraisal of LDV/SOF[11], which used a micro-costing approach, accounting for costs of outpatient appointments, inpatient care, tests and investigations. Unit costs, references used to estimate the monitoring costs in TA363, and proportions of resources used in TA363 are presented in the manufacturer's submission appendices. These are mainly based on the study by Shepherd et al and were validated by clinical experts. [111] The total monitoring costs estimated in TA363 was inflated to 2014/15 using the hospital and community healthcare services (HCHS) index reported in the personal social services research unit (PSSRU) 2015[158]. The same on-treatment monitoring costs are applied to all DAAs such as LDV/SOF, 2D/3D, DCV and EBR/GZR as there is a degree of similarity between DAAs in relation to monitoring timelines. It should be noted that treatment-naive patients have an additional cost of £642.72 for non-cirrhotic and £838.59 for cirrhotic related to their initial evaluation. Further evaluation costs are applicable to both treatment experienced and treatment naïve patients and are presented in Table 77. These costs are consistent between treatments and between C and NC patients, at £480.51. The monitoring costs by indication are summarised in Table 78.

Table 77. Summary of monitoring costs by phase and treatment duration

	Initial evaluation	Further investigation	Monitoring during active treatment (weeks)				
			4	8	12	24	48
Non-cirrhotic							
EBR/GZR	£642.72	£480.51	£627.42	£1,020.19	£1,144.65	£1,392.56	
PR	£642.72	£480.51	£736.58	£987.54	£1,346.65	£1,790.43	£2,626.98
SOF	£642.72	£480.51	£627.42	£750.86	£1,144.65	£1,392.56	
SMV	£642.72	£480.51	£736.58	£987.54	£1,408.88	£1,913.87	
3D	£642.72	£480.51	£627.42	£1,020.19	£1,144.65	£1,392.56	
LDV/SOF	£642.72	£480.51	£627.42	£1,020.19	£1,144.65	£1,392.56	
DCV	£642.72	£480.51	£627.42	£1,020.19	£1,144.65	£1,392.56	
Cirrhotic							
EBR/GZR	£838.59	£480.51	£627.42	£1,022.23	£1,145.67	£1,394.60	
PR	£838.59	£480.51	£736.58	£987.54	£1,473.15	£2,297.46	£3,794.08
SOF	£838.59	£480.51	£627.42	£750.86	£1,145.67	£1,394.60	
SMV	£838.59	£480.51	£736.58	£987.54	£1,535.38	£2,421.93	
3D	£838.59	£480.51	£627.42	£1,022.23	£1,145.67	£1,394.60	
LDV/SOF	£838.59	£480.51	£627.42	£1,022.23	£1,145.67	£1,394.60	
DCV	£838.59	£480.51	£627.42	£1,022.23	£1,145.67	£1,394.60	

Abbreviations. 3D: ombitasvir/paritaprevir/ritonavir+dasabuvir; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR, peginterferon plus ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 78. Summary of monitoring costs per treatment regimen and per subgroups

Treatment	Duration (weeks)	Cost (£)											
		Genotype 1a				Genotype 1b				Genotype 4			
		TN		TE		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
GZB/EBR	12	£2,465	£2,268	£1,626	£1,625	£2,465	£2,268	£1,626	£1,625	£2,465	£2,268	£1,626	£1,625
BSC	0	N/A	£0	N/A	£0	N/A	£0	N/A	£0	N/A	£0	N/A	£0
PR	48	£5,113	£3,750	£4,275	£3,107	£5,113	£3,750	£4,275	£3,107	£5,113	£3,750	£4,275	£3,107
SOF	SOF12PR12	£2,465	£2,268	£1,626	£1,625	£2,465	£2,268	£1,626	£1,625	£2,465		£1,626	
SMV	SMV12PR24	£3,741	£3,037	£2,902	£2,394	£3,741	£3,037	£2,902	£2,394	£3,741	£3,037	£2,902	£2,394
2D/3D	3D12RBV12		£2,268		£1,625	£2,465		£1,626					
	3D24RBV24	£2,714		£1,875									
	3D12						£2,268		£1,625				
	2D12RBV12										£2,268		£1,625
	2D12RBV24									£2,714		£1,875	
LDV/SOF	8		£2,143				£2,143						
	12	£2,465		£1,626	£1,625	£2,465		£1,626	£1,625	£2,465		£1,626	£1,625
DCV	DCV12SOF12		£2,268		£1,625		£2,268		£1,625				£1,625
	DCV24PR24									£2,714	£2,516	£1,875	£1,873

Abbreviations. 2D, ombitasvir/paritaprevir/ritonavir; 3D, ombitasvir/paritaprevir/ritonavir+dasabuvir; BSC, best supportive care; C, cirrhotic; DCV, daclatasvir; GZB/EBR, grazoprevir/elbasvir; LDV/SOF, Ledipasvir/Sofosbuvir; NC, non-cirrhotic; PR, peginterferon plus ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, Sofosbuvir; TE, treatment experienced; TN, treatment naïve

5.5.6 Health-state unit costs and resource use

The health state costs associated with HCV patients in each health state were obtained from the SLR described in section 5.1 and reported in appendix 21. Most of these health state costs are sourced from the Wright et al UK study[23] (i.e. F0; F1; F2; F3; F4; DC; HCC) and from the Grishchenko 2009 (i.e. SVR F0; SVR F1; SVR F2; SVR F3; SVR F4) [112].The liver transplant health state costs (i.e. liver transplant, liver transplant care; post liver transplant) were sourced from the Longworth publication[159] as it is the original publication referenced in the Wright et al study [23]. All the health states costs sourced from the aforementioned publications were inflated to 2014/15 values using the HCHS index of the 2015 PSSRU publication[158] (see Table 79). The original Wright et al study [23]was referenced in diverse publications [26, 111, 121, 124, 130, 149, 160]. The same costs were applied to treatment-naïve, treatment-experienced patients as well as GT1a, GT1b and GT4 patients.

Based on clinical expert opinion, non-cirrhotic patient who achieve SVR are assumed to incur costs for one additional cycle to reflect required monitoring. In cirrhotic patients who achieve SVR as monitoring is assumed to be for the lifetime of the patient the SVR health state cost is applied until death.

Table 79. Health state costs (inflated)

Cost Parameter	Mean	SE	Reference
SVR, F0	£237.01	£27.71	Grishchenko et al, 2009 [112]
SVR, F1	£237.01	£27.71	
SVR, F2	£289.81	£33.88	
SVR, F3	£289.81	£33.88	
SVR, F4	£512.75	£59.94	
F0	£189.27	£157.73	Wright et al, 2006 [23]
F1	£189.27	£157.73	
F2	£983.40	£104.33	
F3	£983.40	£104.33	
F4	£1,560.82	£307.23	
DC	£12,508.53	£2,083.38	
HCC	£11,146.58	£2,619.42	
LT - liver transplant	£37,484.43	£3,956.63	Longworth et al 2001[159]
LT - care in year in which transplant occurs	£12,972.11	£3,494.66	
PLT	£1,899.60	£486.93	

Abbreviations. DC: decompensated cirrhosis; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis; HCC: hepatocellular carcinoma; LD: liver disease; LT: liver transplant (1st year); PLT: post liver transplant (subsequent years); SVR: sustained-virologic response

5.5.7 Adverse reaction unit costs and resource use

The model accounts for the different drugs used to treat each of the treatment-related AEs. Frequencies for each AE attributed to the use of EBR/GZR and comparators are presented

in Table 67. The assumptions made on the AE treatment dosing and duration are based on the previous appraisal of LDV/SOF[11] and TVR [38] (see Table 80), and used alongside the drug costs per pack to calculate the total treatment costs for each event (Table 81). The assumptions made on the treatment regimen and respective duration required to treat AEs were validated by UK clinical experts during the previous submissions. The unit costs of each drug were updated using the most recent sources MIMS and eMit.[16, 156]

Table 80. Adverse event treatment dosing and duration

	Drug (drug name)/treatment	Unit dose	% treated	Weeks of treatment	Source
Anaemia	Epoetin alfa (Eprex®)	40,000 units/wk	1%	4	TA363, 2015[11]
Anaemia	Blood transfusion	N/A	0.70%	N/A	
Neutropenia	Filgrastim (Neupogen®)	395 µg/d	100%	2	
Rash	Hydrocortisone 1% cream	15 g	100%	4	TA363, 2015 TA252, 2012[11, 38]
Pruritus	Chlorphenamine (Piriton®)	16 mg/d	100%	4	
Nausea	Metoclopramide	30 mg/d	100%	4	

Abbreviations. d: day; wk: week

Table 81. Adverse event unit costs

	Drug (drug name)/treatment	Drug cost per pack	Unit dose	Quantity per pack	Source
Anaemia	Epoetin alfa (Eprex®)	£265.48	40,000 units/wk	1	MIMS[16]
Anaemia	Blood transfusion	£1,037.10	N/A	N/A	NHS Ref costs 2014-15 [155]
Neutropenia	Filgrastim (Neupogen®)	£263.52	395 µg/d	5	MIMS[16]
Rash	Hydrocortisone 1% cream	£0.51	15 g	1	eMit[156]
Pruritus	Chlorphenamine (Piriton®)	£0.21	16 mg/d	28	
Nausea	Metoclopramide	£0.26	30 mg/d	28	

Abbreviations. d: day; epo: erythropoietin; wk: week

In the SOF economic model [10] it was assumed that most AEs would be dealt with as outpatient visits as opposed to inpatient visits, based on KOL opinion. The outpatient costs were split into specialist and outpatient visits to reflect the type of care provided to manage the AE (see Table 82-Table 83). This assumption was also implemented in the EBR/GZR economic model. Each visit is assumed to last 20 minutes. The unit costs were updated based on the NHS England Reference costs 2014-2015 [155] and PSSRU unit costs 2015 [158].

Table 82. Other adverse event costs: Outpatient costs

	% outpatient visits	Number of outpatient visit	Cost per outpatient visit	Total outpatient cost	Source
Anaemia (Epo)	100%	6	£41.00	£246.00	PSSRU unit costs 2015 – Hospital registrar group[155]
Anaemia (Blood transfusion)	0%	0	£0.00	£0.00	KOL opinion – TA363[11]
Neutropenia	100%	6	£41.00	£246.00	PSSRU unit costs 2015 – Hospital registrar group[155]
Rash	100%	4	£41.00	£164.00	

	% outpatient visits	Number of outpatient visit	Cost per outpatient visit	Total outpatient cost	Source
Pruritus	0%	0	£0.00	£0.00	KOL opinion – TA363[11]
Nausea	0%	0	£0.00	£0.00	

Abbreviations. d: day; wk: week

Table 83. Other adverse event costs: Specialist costs

	% specialist visits	Number of specialist visits	Cost per specialist visit (£)	Total societal cost (£)	Source
Anaemia (Epo)	50%	1	£223.35	£111.67	NHS Ref costs 2014-15 (NHS 2015) [155]
Aneamia (blood transfusion)	50%	1	£223.35	£111.67	
Neutropenia	50%	1	£223.35	£111.67	
Rash	100%	2	£223.35	£446.70	
Pruritus	0%	0	£0.00	£0.00	KOL opinion – TA363 [11]
Nausea	0%	0	£0.00	£0.00	

Abbreviations. d: day

5.5.8 Miscellaneous unit costs and resource use

There are no additional costs included in the model apart from those outlines in the previous sections.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Tabulated variables included in the cost-effectiveness analysis

Please find in Appendix 18 a summary of the variables applied in the economic model.

5.6.2 For the base-case de novo analysis the company should ensure that the cost-effectiveness analysis reflects the NICE reference case as closely as possible

The base-case cost-effectiveness analysis reflects the NICE reference case.

5.6.3 List of all assumptions used in the de novo economic model with justifications for each assumption

Table 84: Model assumptions

Assumption	Justification
Patients in chronic HCV states health states (including the states of mild disease, HCV F0 and F1) cannot spontaneously clear HCV.	The likelihood of a chronically infected person spontaneously clearing HCV is very small. This is consistent with previous HCV models submitted to NICE. [10-13, 40]
There is no progression to more severe health states (i.e. cirrhosis) while patients are on-treatment.	This is consistent with previous HCV models submitted to NICE. ([10-13, 40]
Treatment stopping rules are captured by the discontinuation rate related to AEs.	Discontinuations related to AEs were taken from the most appropriate trial data and, where available, cessation of treatment was modelled in line with the timing of discontinuations reported in each of the trials. This is consistent with previous HCV models submitted to NICE. [10-13, 40]
Achieving SVR is considered a cure for patients who were originally non-cirrhotic (i.e. baseline fibrosis score of F0, F1, F2 or F3).	This is consistent with end of treatment biopsies from previously reported trials that did not find any evidence of disease progression following an SVR. [161]
Previously cirrhotic patients (i.e. baseline fibrosis score of F4) are assumed to have an excess risk of DC and HCC even if they have achieved SVR.	This is related to the persistent risk of developing DC and HCC. [141, 142] Most previous HCV models submitted to NICE considered this either in base case or in a sensitivity analysis .[10-13, 40]
The health state DC which consists of multiple outcomes (i.e. ascites, variceal hemorrhage, and encephalopathy) is aggregated into one health state.	These decompensation modes are not mutually exclusive. This is consistent with previous HCV models submitted to NICE.[10-13, 40]
Progression to DC only occurs in cirrhotic patients (health states of compensated cirrhosis)	This is consistent with previous HCV models submitted to NICE. [10-13, 40]
Progression to HCC only occurs in cirrhotic patients (health states of compensated or decompensated cirrhosis). This excludes the risk of HCC even among patients with advanced fibrosis F3.	This is consistent with previous HCV models submitted to NICE .[10-13, 40]
The probability of progressing to liver transplant is possible from DC or HCC health state only	This is consistent with previous HCV models submitted to NICE. [10-13, 40]
Patients who receive a liver transplant are assumed to be at no risk of reactivation and progression to liver disease (i.e. there are no risks for fibrosis, DC, HCC or need for re-transplantation).	This is consistent with previous HCV models submitted to NICE.[10-13, 40]
Patients with compensated cirrhosis face the same mortality risk (i.e. no excess mortality risk) as the general population (i.e. no liver-related death).	This is consistent with previous HCV models submitted to NICE. [10-13, 40]
Future re-treatment of patients who do not achieve SVR is not considered. There are	This is consistent with previous HCV models submitted to NICE.[10-13, 40]

Assumption	Justification
no long-term benefits of treatment for patients who relapsed or did not respond.	
In some genotypes, daclatasvir is recommended by NICE only if the person has significant fibrosis (i.e. F3, F4). In these instances it is assumed that the recommendation applies to all non-cirrhotic patients (i.e. F0-F3) and cirrhotic patients (i.e. F4).	All NICE recommendations on DAAs were split according to cirrhosis stage. Daclatasvir is the only DAA recommended in a subpart of the non-cirrhotic patients (i.e. F3). [12] Therefore, to facilitate the decision making process, the F3 recommendation is applied to all non-cirrhotic patients.
Clinical efficacy assumptions (i.e. SVR rates) are required for some comparators when data is not available from the published literature.	In the absence of the SVR values relevant to the decision problem for comparator data MSD has made an assumption that considers the patients genotype, cirrhosis stage, and treatment experience. i.e. in the absence of GT1a or GT1b data, MSD applies GT1 overall data split by C or NC and treatment experience, when possible.
Cirrhotic patients who have achieved SVR incur costs for a period of 5 years; whereas non-cirrhotic who have achieved SVR incur costs for 1 year.	The cirrhotic patients who achieve SVR have a higher risk of progressing to more severe health states (i.e. DC, HCC) hence they need to be followed for a longer period of time. This is consistent with previous HCV models submitted to NICE [10-13, 40]
Utility decrement for 2D/3D is assumed the same as EBR/GZR.	In the absence of 2D/3D data, a conservative approach of utilising EBR/GZR data was applied.
GT1 clinical efficacy data used in base case for GT4.	related to limited GT4 data, GT1a data were used as proxy for GT4. This approach was accepted in previous HCV models submitted to NICE[11, 13] and it was reinforced by clinical expert opinion.

Abbreviations. DC: decompensated cirrhosis; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis; HCC: hepatocellular carcinoma; HCV: Hepatitis C virus; LD: liver disease; LT: liver transplant (1st year); PLT: post liver transplant (subsequent years); SVR: sustained-virologic response

5.7 Base-case results

5.7.1 Base-case cost effectiveness analysis results

The NMA revealed no significant differences between EBR/GZR and the other all-DAA regimens (LDV/SOF, 2D/3D, and DCV+SOF) in any of the subgroups that were investigated. As such, MSD does not believe that comparison across new DAAs based on efficacy is justified. Therefore, a pairwise comparison the DAAs versus PR is presented in this section and the full incremental analysis in appendix 22.

Given its historic use to treat cirrhotic HCV patients, an imputed PR arm was created to allow the formation of a network thus allowing comparative analyses (see section 4.10). Consequently, PR is used as a comparator in the cirrhotic subpopulations to enable pairwise comparisons with EBR/GZR and comparators.

The results of the economic model are presented in section 5.7.2.

5.7.2 Base-case incremental cost effectiveness analysis results

Table 85 to Table 96 present the base case pairwise incremental cost-effectiveness results for comparisons of EBR/GZR and its relevant comparators versus PR across the different populations. It should be noted that the results, ranked by costs, are based on EBR/GZR and comparators list prices (given the lack of information publicly available on comparators CMU prices, when applicable), therefore MSD is not able to accurately capture the cost-effectiveness of EBR/GZR or the recently approved DAAs. The results should therefore be considered indicative and not reflective of the current HCV commercial landscape.

Table 85. Base case results – GT1a TN C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,599	15.526	7.741	-	-	-	-
SOF	£64,907	16.928	8.845	£10,308	1.402	1.104	£9,338
SMV	£65,380	16.384	8.456	£10,781	0.858	0.714	£15,095
EBR/GZR	£68,555	17.498	9.260	£13,956	1.973	1.518	£9,193
LDV/SOF	£70,941	17.498	9.259	£16,342	1.972	1.518	£10,765
2D/3D	£96,765	17.435	9.208	£42,166	1.909	1.467	£28,742

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 86. Base case results – GT1a TN NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,580	20.781	13.473	-	-	-	-
BSC	£30,513	19.183	11.404	£3,932	-1.598	-2.069	Dominated
LDV/SOF	£32,059	21.663	15.098	£5,479	0.882	1.625	£3,371
SMV	£36,693	21.360	14.550	£10,113	0.579	1.077	£9,388
2D/3D	£40,479	21.757	15.225	£13,899	0.976	1.752	£7,935
EBR/GZR	£42,389	21.707	15.150	£15,809	0.926	1.677	£9,427
SOF	£43,855	21.590	14.942	£17,275	0.809	1.469	£11,762
DCV+SOF	£64,902	21.757	15.217	£38,321	0.976	1.744	£21,976

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 87. Base case results – GT1a TE C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£55,175	14.627	7.447	-	-	-	-
SMV	£61,679	16.035	8.592	£6,504	1.407	1.145	£5,681
SOF	£65,426	15.867	8.513	£10,252	1.240	1.066	£9,616
EBR/GZR	£67,287	16.663	9.116	£12,113	2.036	1.669	£7,257
LDV/SOF	£69,467	16.694	9.139	£14,292	2.067	1.692	£8,448
2D/3D	£94,679	16.742	9.160	£39,504	2.115	1.713	£23,062

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

Table 88. Base case results – GT1a TE NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£27,836	19.504	12.806	-	-	-	-
BSC	£28,835	18.315	11.271	£999	-1.189	-1.535	Dominated
SMV	£34,982	20.224	14.203	£7,146	0.720	1.398	£5,112
2D/3D	£39,915	20.466	14.713	£12,079	0.962	1.907	£6,334
EBR/GZR	£42,298	20.383	14.578	£14,462	0.879	1.773	£8,159
LDV/SOF	£43,747	20.466	14.713	£15,911	0.962	1.907	£8,343
SOF	£45,111	20.170	14.198	£17,275	0.666	1.393	£12,403
DCV+SOF	£64,599	20.445	14.670	£36,763	0.940	1.864	£19,718

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

Table 89. Base case results – GT1b TN C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,884	15.478	7.709	-	-	-	-
SOF	£62,628	17.310	9.107	£7,743	1.833	1.398	£5,538
2D/3D	£64,947	17.596	9.327	£10,062	2.119	1.618	£6,217
SMV	£65,571	16.352	8.434	£10,687	0.874	0.725	£14,741
EBR/GZR	£67,714	17.640	9.356	£12,829	2.162	1.647	£7,787
LDV/SOF	£70,320	17.602	9.331	£15,436	2.125	1.622	£9,517

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 90. Base case results – GT1b TN NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,800	20.761	13.442	-	-	-	-
BSC	£30,513	19.183	11.404	£3,712	-1.578	-2.039	Dominated
LDV/SOF	£31,899	21.678	15.120	£5,099	0.917	1.678	£3,039
SMV	£37,062	21.326	14.499	£10,262	0.565	1.057	£9,710
2D/3D	£40,232	21.772	15.246	£13,432	1.011	1.804	£7,446
EBR/GZR	£41,963	21.746	15.209	£15,162	0.986	1.766	£8,585
SOF	£42,161	21.746	15.175	£15,361	0.985	1.733	£8,865
DCV+SOF	£65,018	21.747	15.201	£38,218	0.986	1.758	£21,739

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 91. Base case results – GT1b TE C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,008	14.805	7.577	-	-	-	-
SMV	£59,760	16.328	8.806	£5,751	1.522	1.229	£4,680
2D/3D	£62,754	16.892	9.285	£8,746	2.087	1.708	£5,122
EBR/GZR	£65,304	16.966	9.337	£11,296	2.160	1.760	£6,418
SOF	£66,777	15.661	8.363	£12,769	0.855	0.786	£16,253
LDV/SOF	£67,689	16.966	9.337	£13,681	2.160	1.760	£7,773

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

Table 92. Base case results – GT1b TE NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£28,407	19.458	12.730	-	-	-	-
BSC	£28,835	18.315	11.271	£428	-1.143	-1.459	Dominated
SMV	£35,177	20.208	14.178	£6,770	0.750	1.448	£4,676
2D/3D	£38,905	20.541	14.835	£10,499	1.083	2.105	£4,988
EBR/GZR	£40,595	20.522	14.804	£12,188	1.064	2.074	£5,877
LDV/SOF	£43,060	20.522	14.804	£14,654	1.064	2.074	£7,066
SOF	£44,393	20.229	14.293	£15,987	0.771	1.564	£10,225
DCV+SOF	£63,650	20.522	14.796	£35,244	1.064	2.066	£17,060

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

Table 93. Base case results – GT4 TN C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,599	15.526	7.741	-	-	-	-
SOF	£63,401	17.181	9.018	£8,802	1.655	1.277	£6,894
SMV	£65,380	16.384	8.456	£10,781	0.858	0.714	£15,095
EBR/GZR	£68,555	17.498	9.260	£13,956	1.973	1.518	£9,193
LDV/SOF	£70,941	17.498	9.259	£16,342	1.972	1.518	£10,765
DCV/PR	£84,350	17.665	9.301	£29,750	2.139	1.560	£19,076
2D/3D	£93,333	17.544	9.282	£38,734	2.018	1.541	£25,138

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 94. Base case results – GT4 TN NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,580	20.781	13.473	-	-	-	-
BSC	£30,513	19.183	11.404	£3,932	-1.598	-2.069	Dominated
SMV	£36,693	21.360	14.550	£10,113	0.579	1.077	£9,388
2D/3D	£37,785	21.757	15.225	£11,204	0.976	1.752	£6,396
EBR/GZR	£42,389	21.707	15.150	£15,809	0.926	1.677	£9,427
DCV/PR	£58,178	21.817	15.207	£31,598	1.036	1.735	£18,217

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TN: treatment-naïve; QALYs, quality-adjusted life years

Table 95. Base case results – GT4 TE C

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,551	14.722	7.517	-	-	-	-
SMV	£61,311	16.091	8.633	£6,760	1.368	1.116	£6,055
SOF	£65,426	15.867	8.513	£10,875	1.145	0.997	£10,911
EBR/GZR	£67,287	16.663	9.116	£12,736	1.940	1.600	£7,962
LDV/SOF	£69,467	16.694	9.139	£14,916	1.972	1.622	£9,194
DCV/PR	£82,894	16.859	9.178	£28,343	2.136	1.662	£17,054
2D/3D	£91,857	16.749	9.164	£37,306	2.027	1.647	£22,645

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

Table 96. Base case results – GT4 TE NC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£27,836	19.504	12.806	-	-	-	-
BSC	£28,835	18.315	11.271	£999	-1.189	-1.535	Dominated
SMV	£34,982	20.224	14.203	£7,146	0.720	1.398	£5,112
2D/3D	£37,220	20.466	14.713	£9,384	0.962	1.907	£4,920
EBR/GZR	£42,298	20.383	14.578	£14,462	0.879	1.773	£8,159
LDV/SOF	£43,747	20.466	14.713	£15,911	0.962	1.907	£8,343
DCV/PR	£57,873	20.515	14.664	£30,037	1.010	1.859	£16,160
DCV+SOF	£64,599	20.445	14.670	£36,763	0.940	1.864	£19,718

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; TE: treatment-experienced; QALYs, quality-adjusted life years

5.7.3 Clinical outcomes from the model

The efficacy data, SVR12, obtained via post-hoc analysis of the included EBR/GZR clinical trials and comparator data as reported in the literature was implemented in the economic model.

5.7.4 Markov traces

Figure 18 to Figure 41 below illustrate how patients move through the model states over time when treated the EBR/GZR and PR regimen, respectively.

The diagrams show that:

- a greater number of patients is in the recovery health states (i.e. “SVR,F0-F3” and “SVR,F4”) following treatment with EBR/GZR than with PR, irrespective of the cirrhotic state. In addition, patients stay longer in these recovery health states following treatment with EBR/GZR than with PR.

- far more cirrhotic patients remain in the cirrhotic health state following treatment with PR than with EBR/GZR.
- patients are more likely to die from liver-related disease following treatment with PR than with EBR/GZR, regardless of the cirrhotic state.

Figure 18. Markov trace for patients with EBR/GZR – GT1a TN C

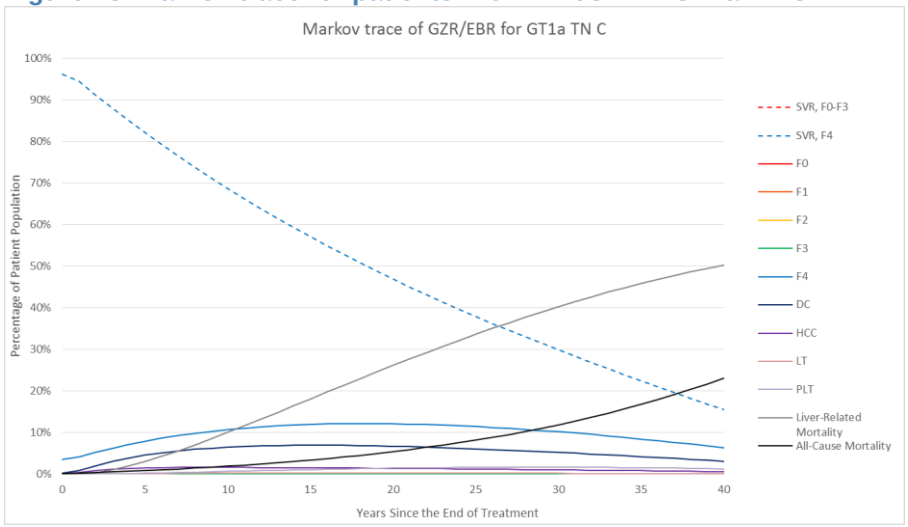


Figure 19. Markov trace for patients with PR – GT1a TN C

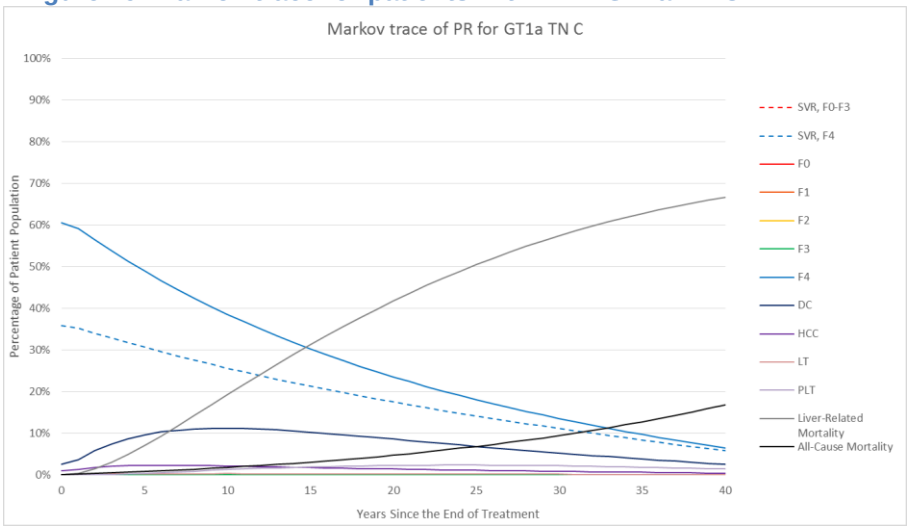


Figure 20. Markov trace for patients with EBR/GZR – GT1a TN NC

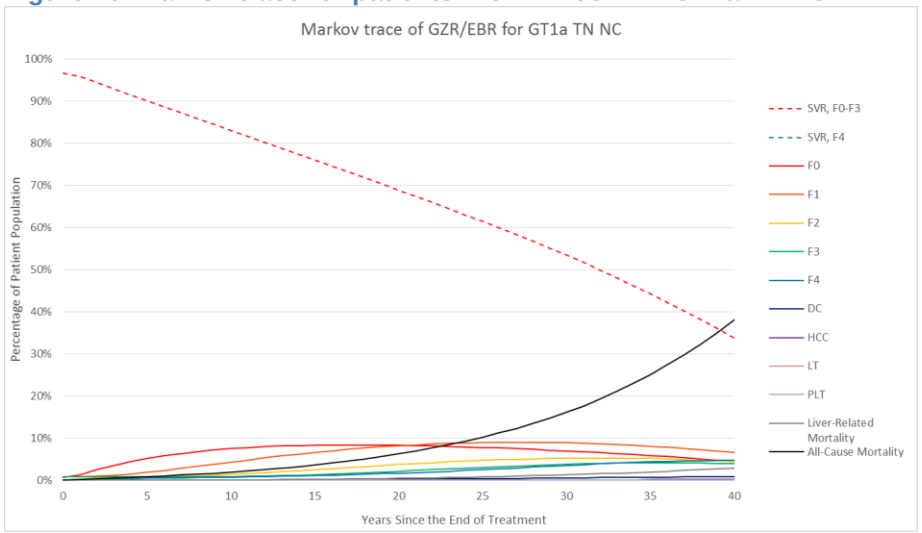


Figure 21. Markov trace for patients with PR – GT1a TN NC

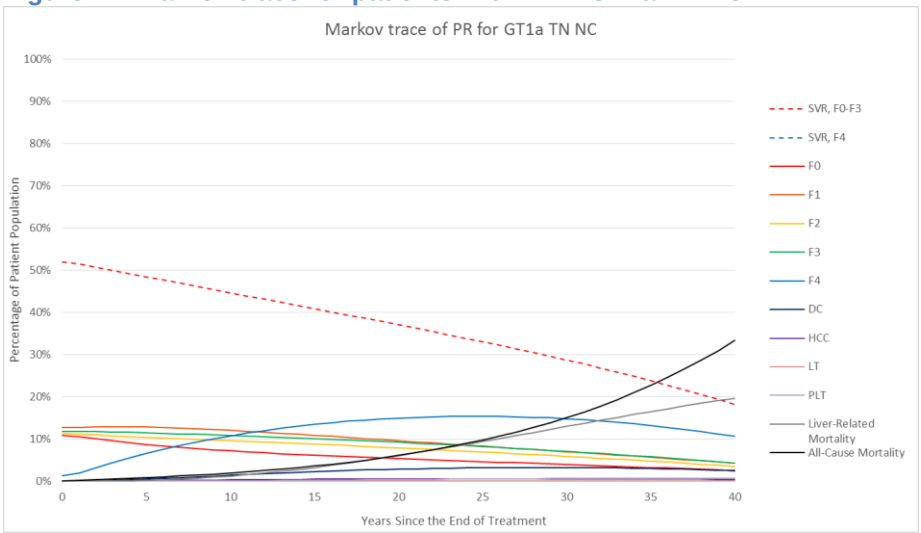


Figure 22. Markov trace for patients with EBR/GZR – GT1a TE C

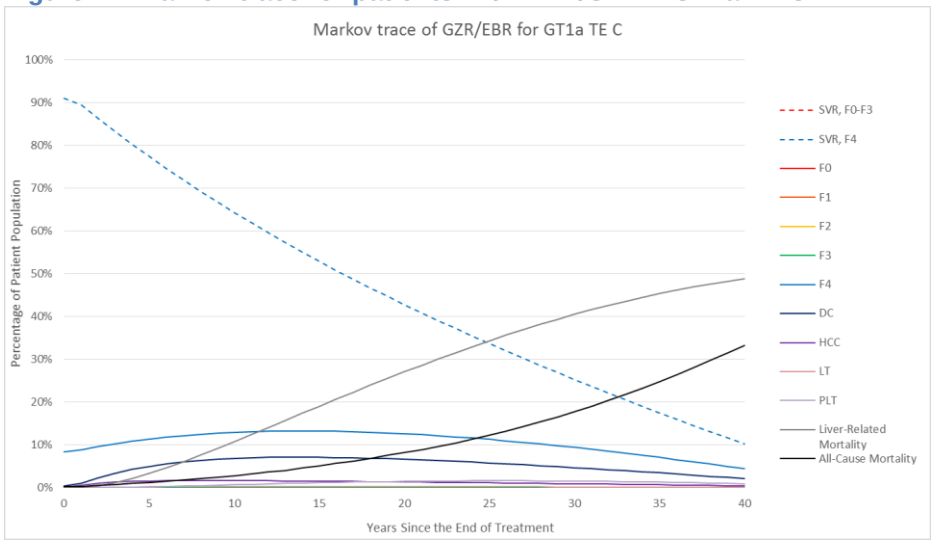


Figure 23. Markov trace for patients with PR – GT1a TE C

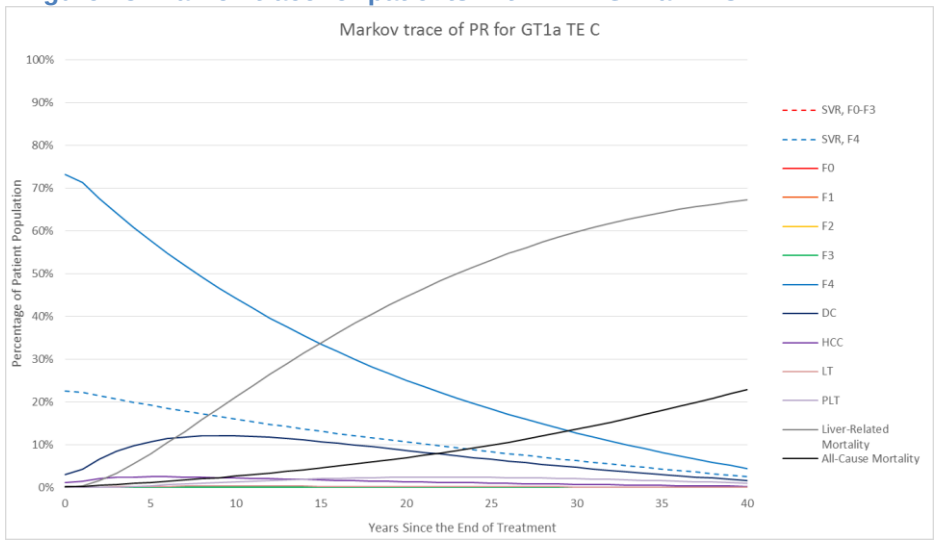


Figure 24. Markov trace for patients with EBR/GZR – GT1a TE NC

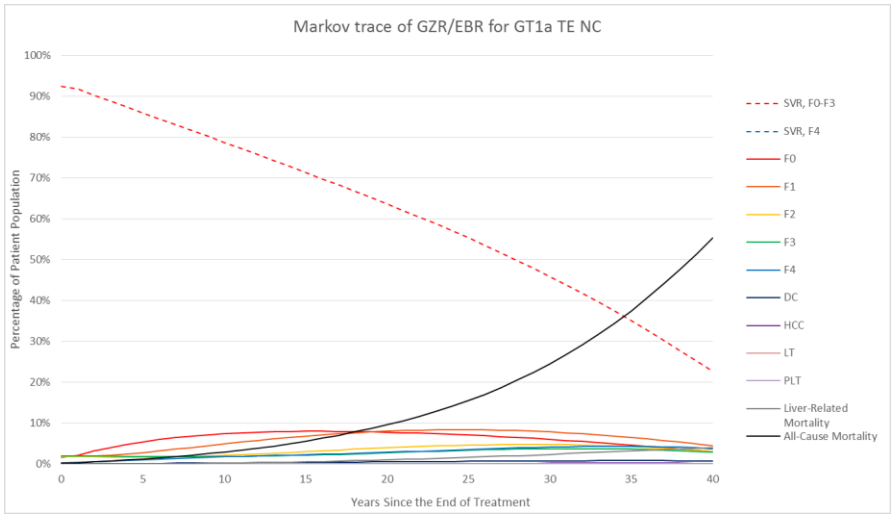


Figure 25. Markov trace for patients with PR – GT1a TE NC

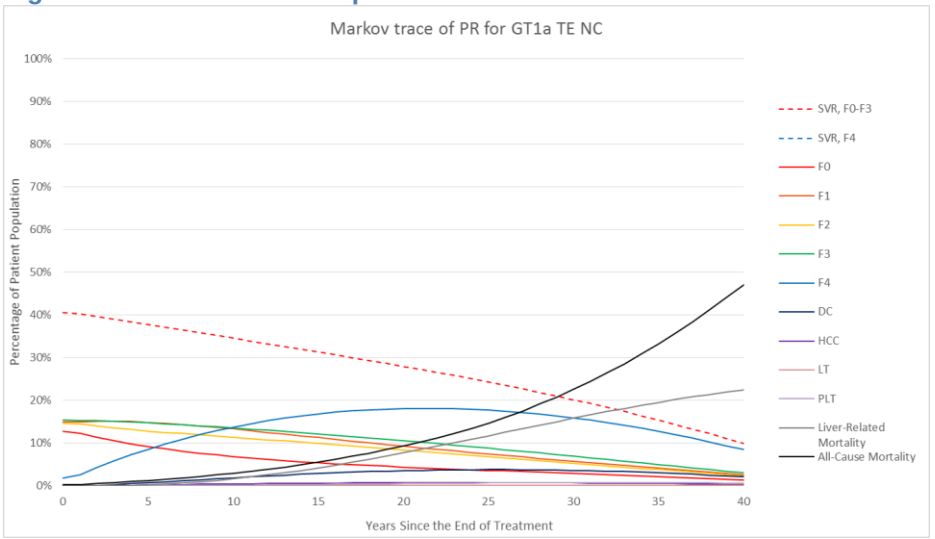


Figure 26. Markov trace for patients with EBR/GZR – GT1b TN C

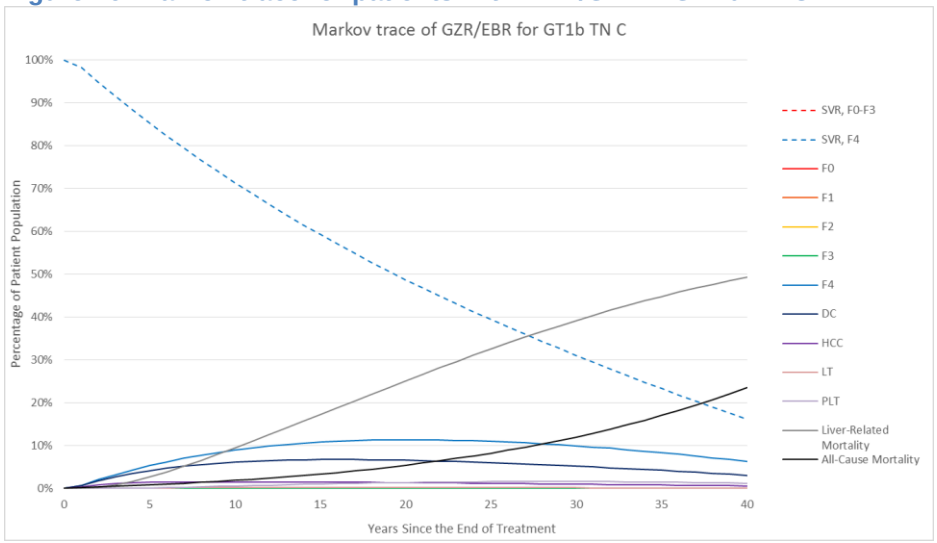


Figure 27. Markov trace for patients with PR – GT1b TN C

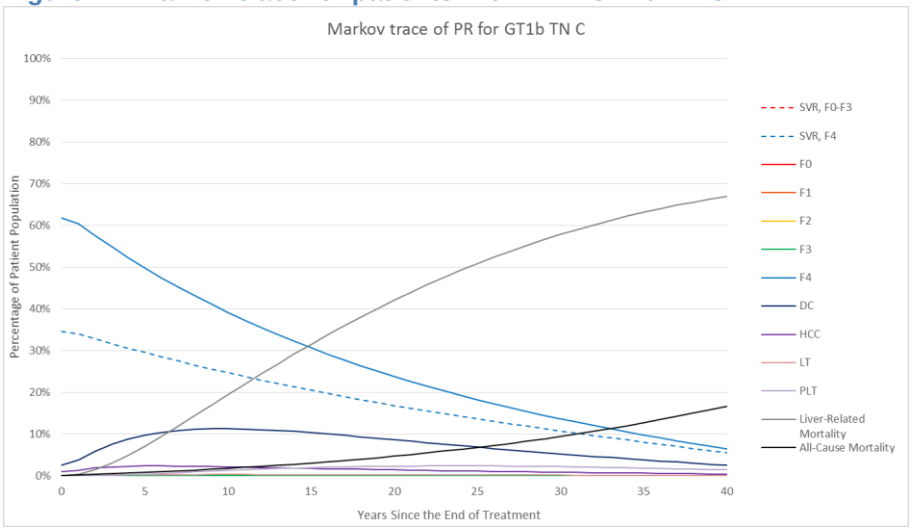


Figure 28. Markov trace for patients with EBR/GZR – GT1b TN NC

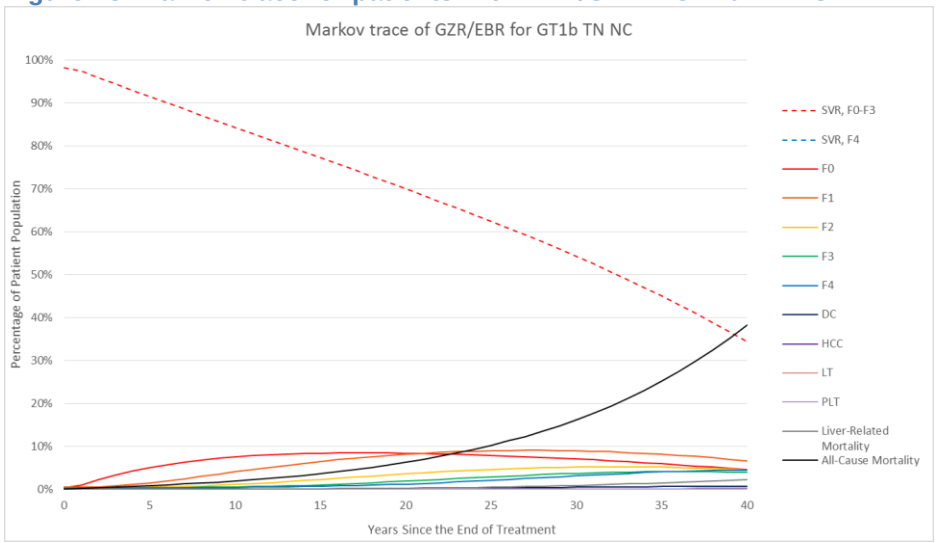


Figure 29. Markov trace for patients with PR – GT1b TN NC

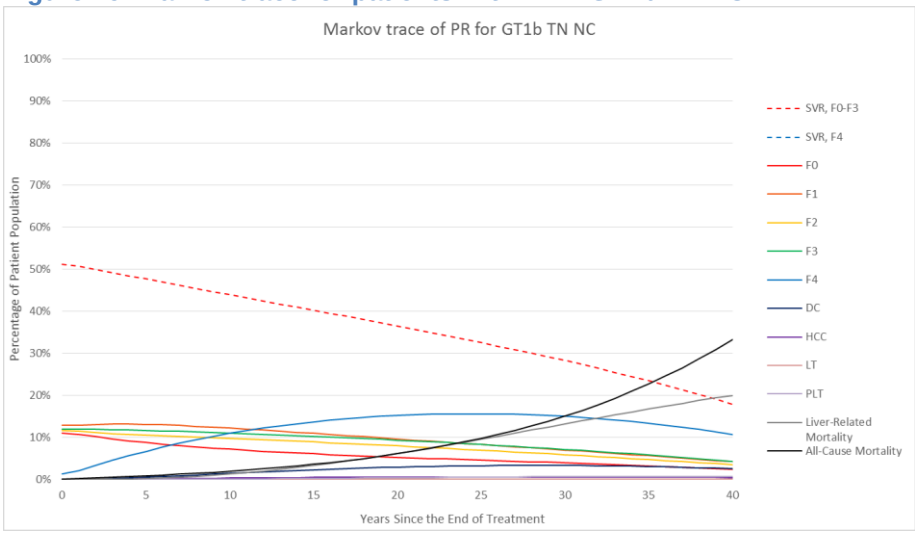


Figure 30. Markov trace for patients with EBR/GZR – GT1b TE C

Figure 31. Markov trace for patients with PR – GT1b TE C

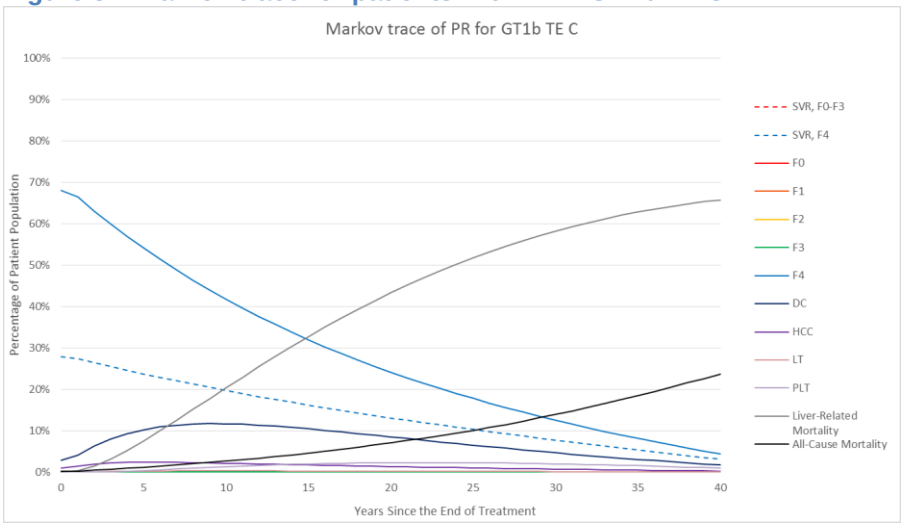


Figure 32. Markov trace for patients with EBR/GZR – GT1b TE NC

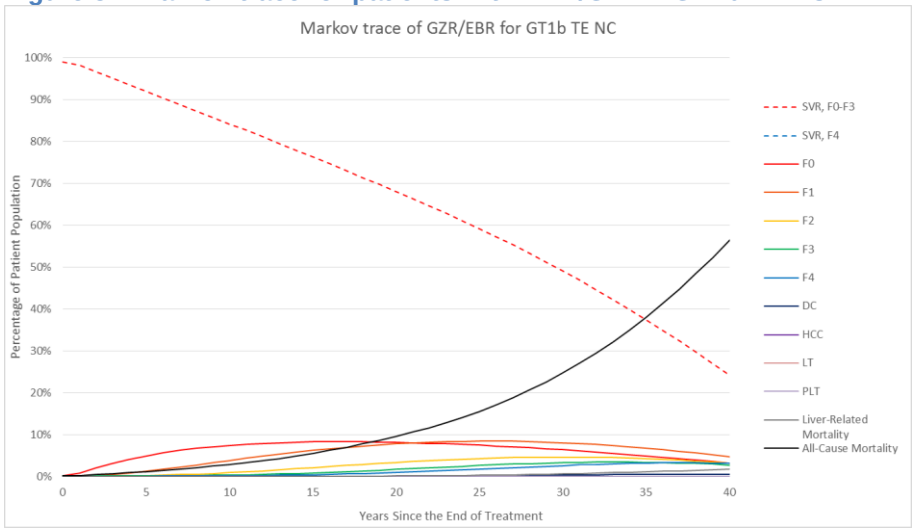


Figure 33. Markov trace for patients with PR – GT1b TE NC

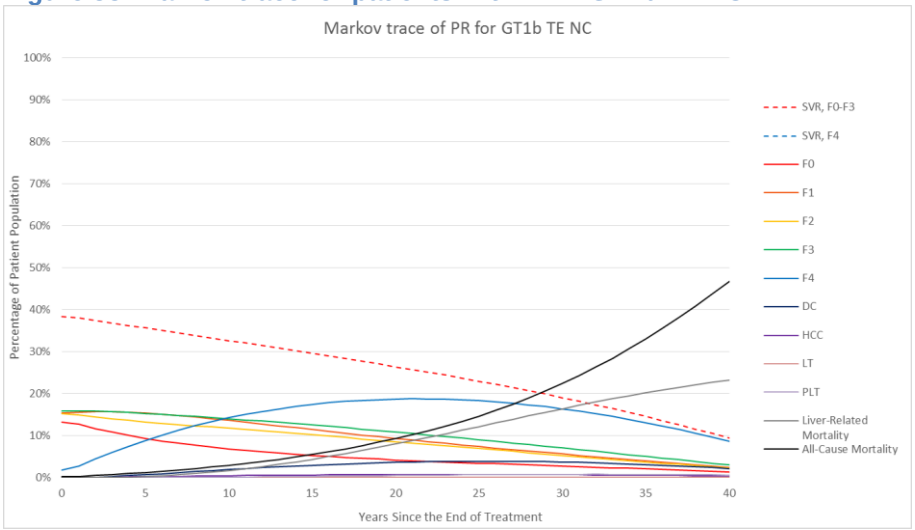


Figure 34. Markov trace for patients with EBR/GZR – GT4 TN C

Figure 35. Markov trace for patients with PR – GT4 TN C

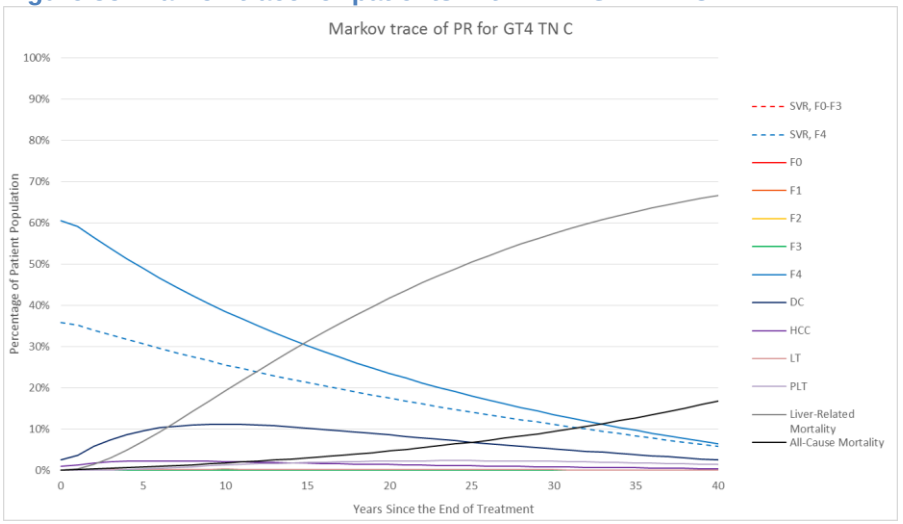


Figure 36. Markov trace for patients with EBR/GZR – GT4 TN NC

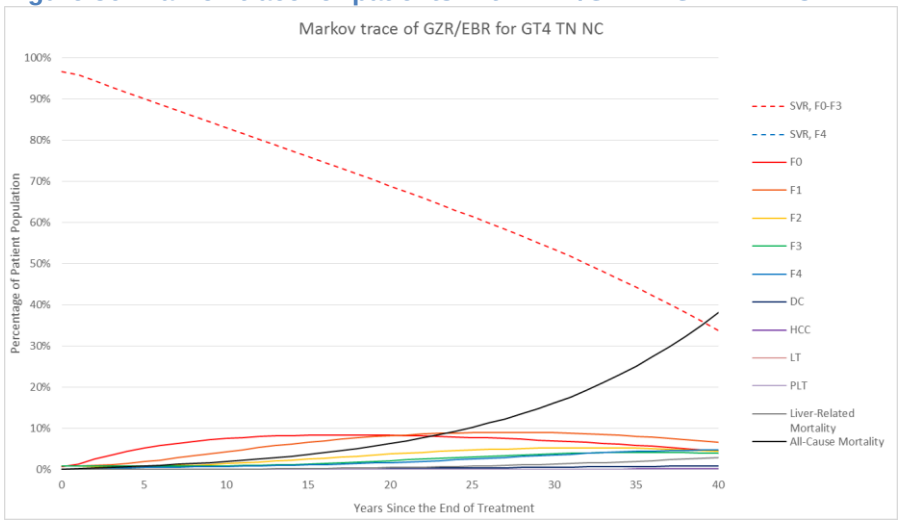


Figure 37. Markov trace for patients with PR – GT4 TN NC

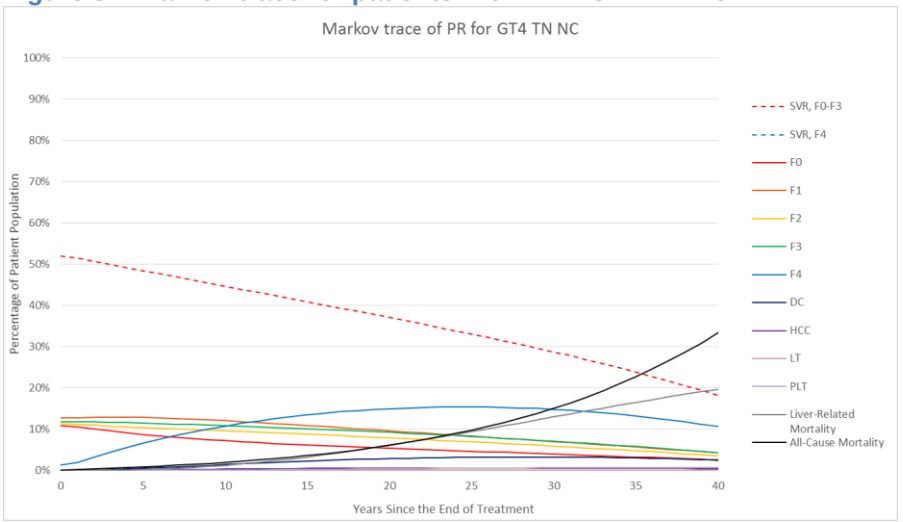


Figure 38. Markov trace for patients with EBR/GZR – GT4 TE C

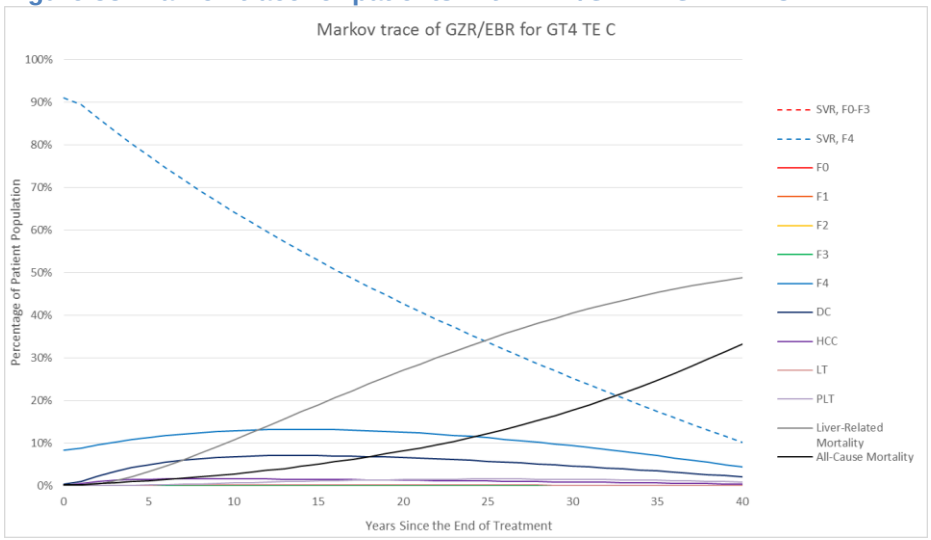


Figure 39. Markov trace for patients with PR – GT4 TE C

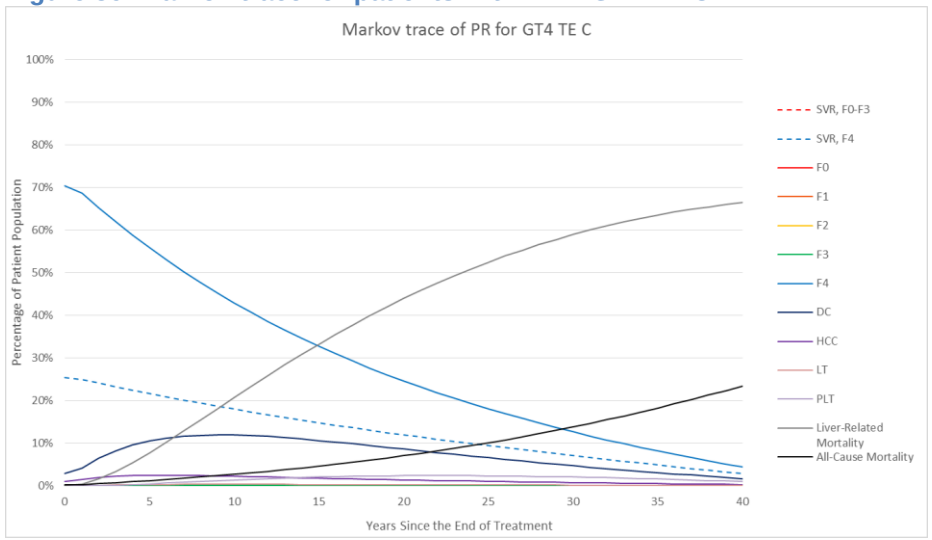


Figure 40. Markov trace for patients with EBR/GZR – GT4 TE NC

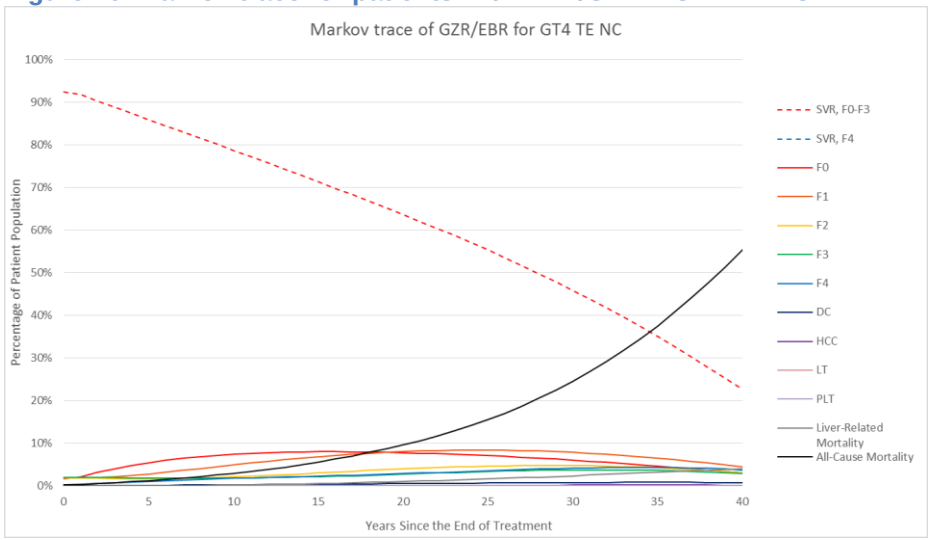
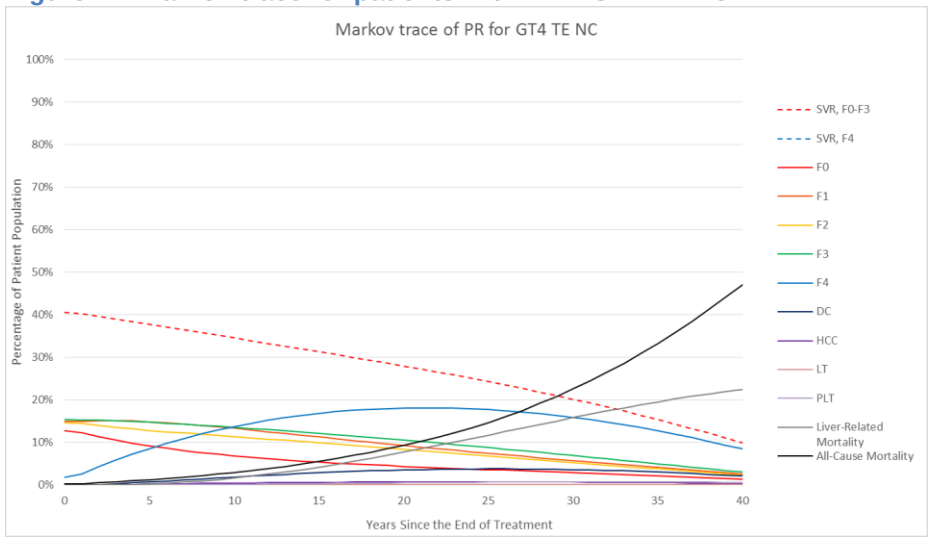


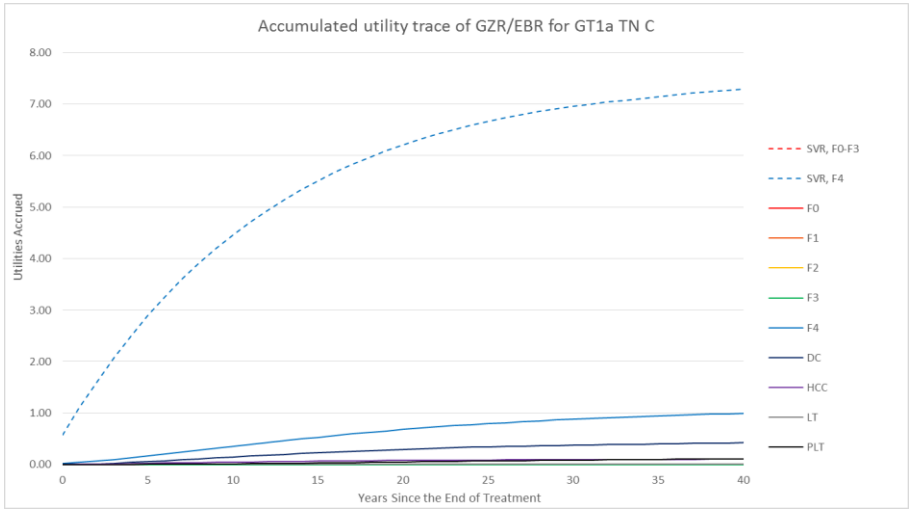
Figure 41. Markov trace for patients with PR – GT4 TE NC

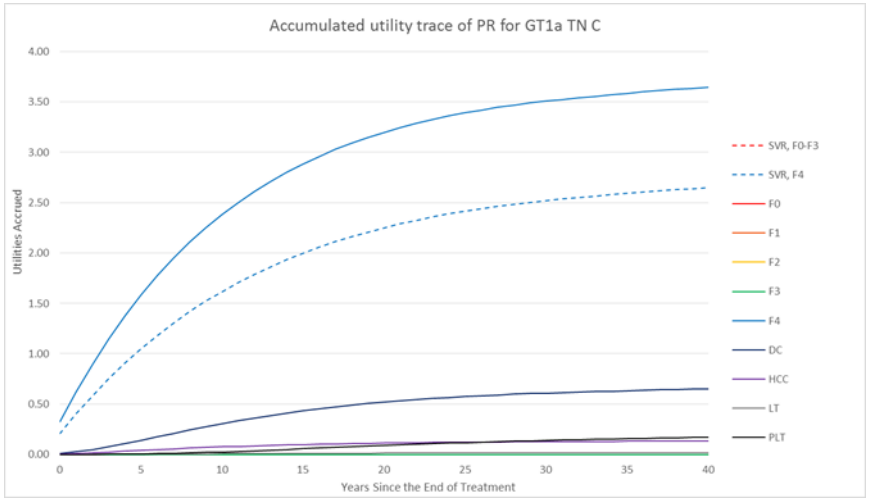


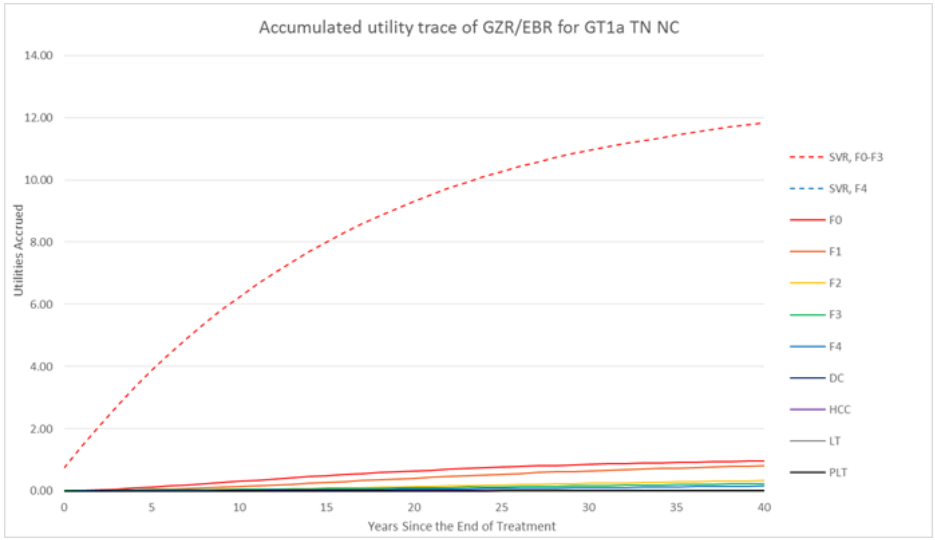
5.7.5 Accrual of QALYs over time

Figure 42 to Figure 47 presented show how the QALYs accumulate over time for EBR/GZR and PR therapies based on patient's cirrhotic status. Patients treated with EBR/GZR accumulate the majority of the QALYs in the SVR health states whereas patients treated with PR accumulate the majority of the QALYs in F0-F4 health states.

Figure 42. Cumulative QALYs over time – GT1a TN C/NC







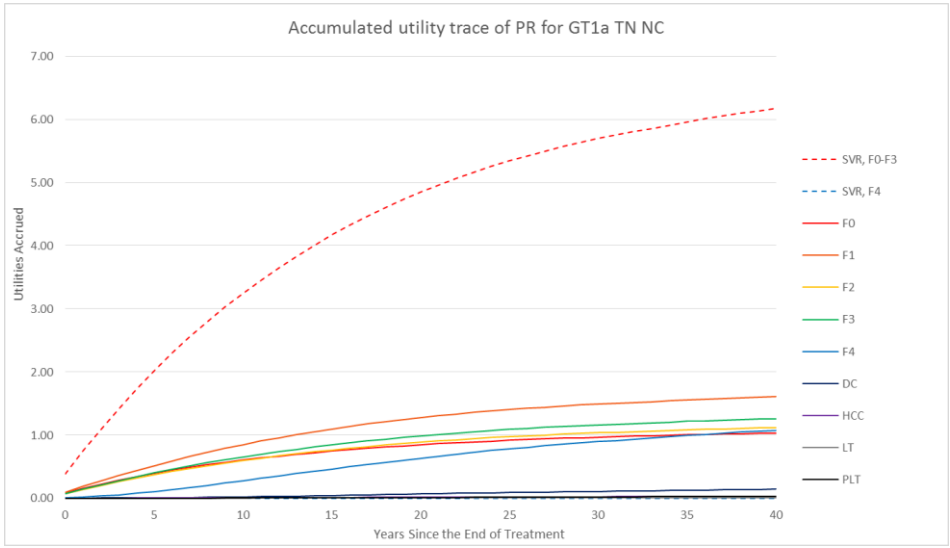
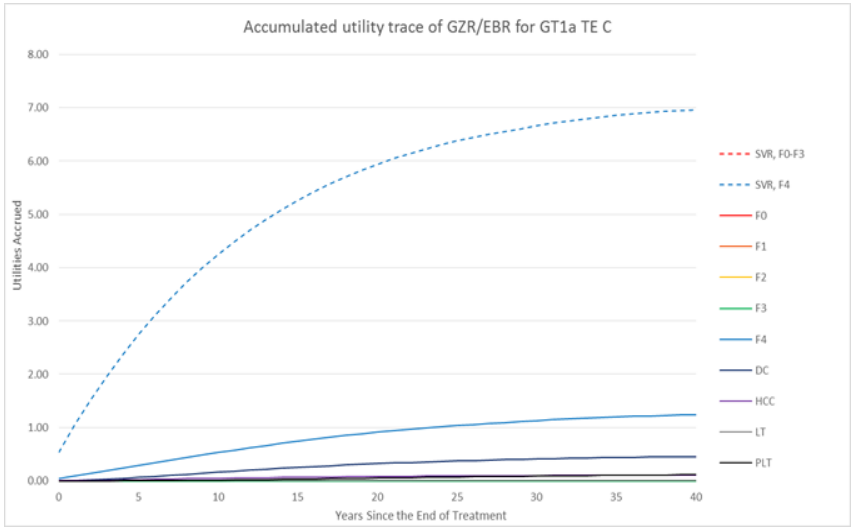
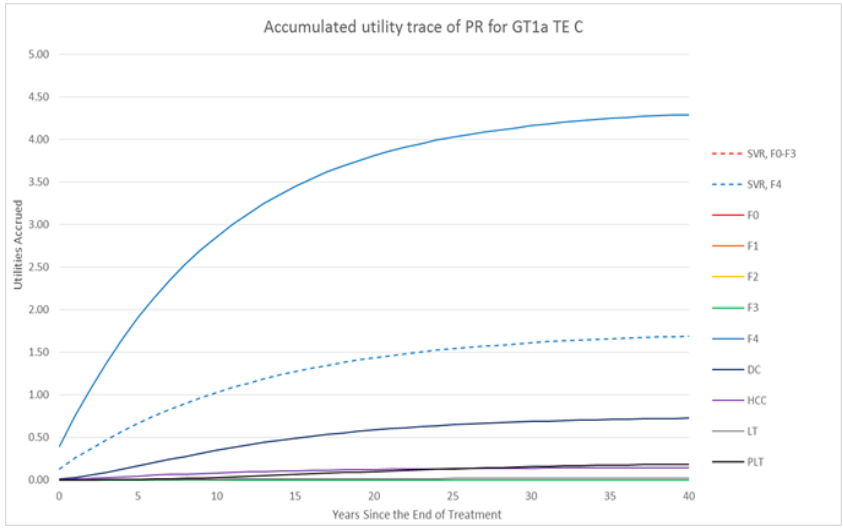
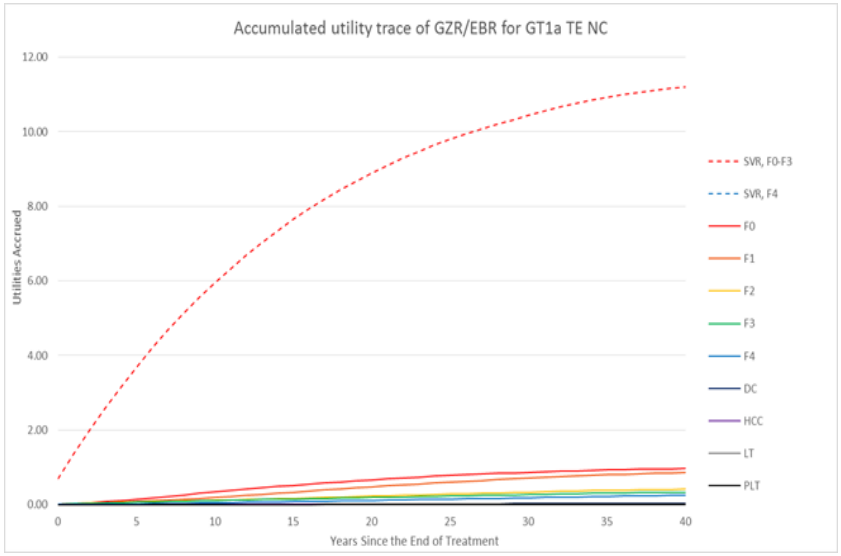


Figure 43. Cumulative QALYs over time – GT1a TE C/NC







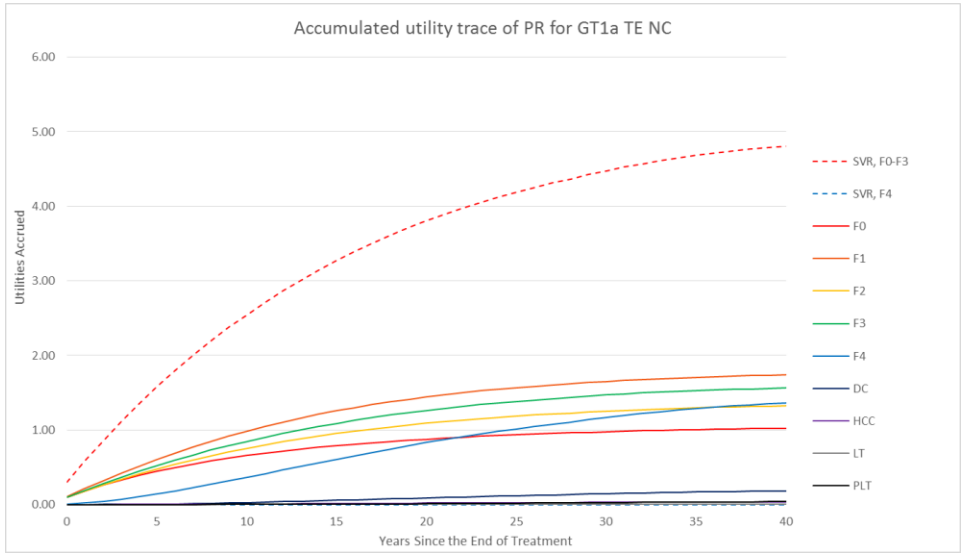
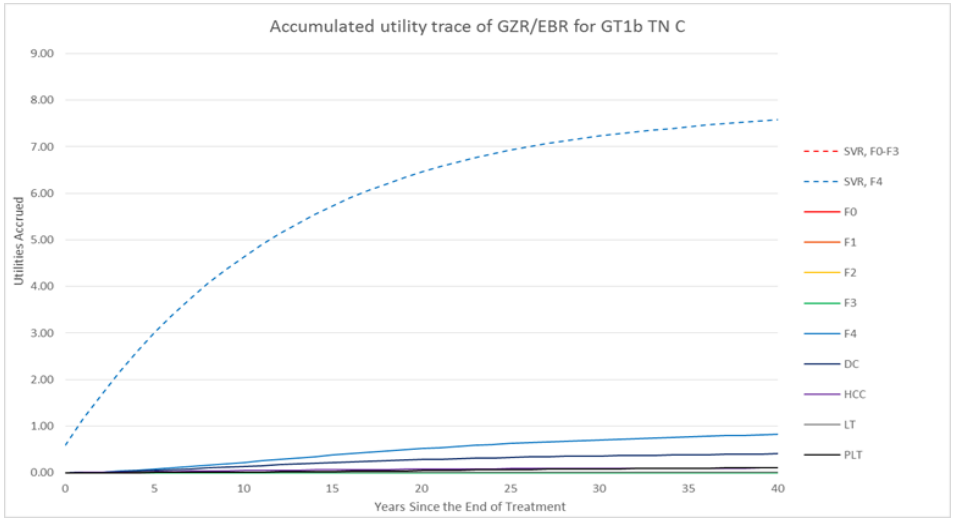
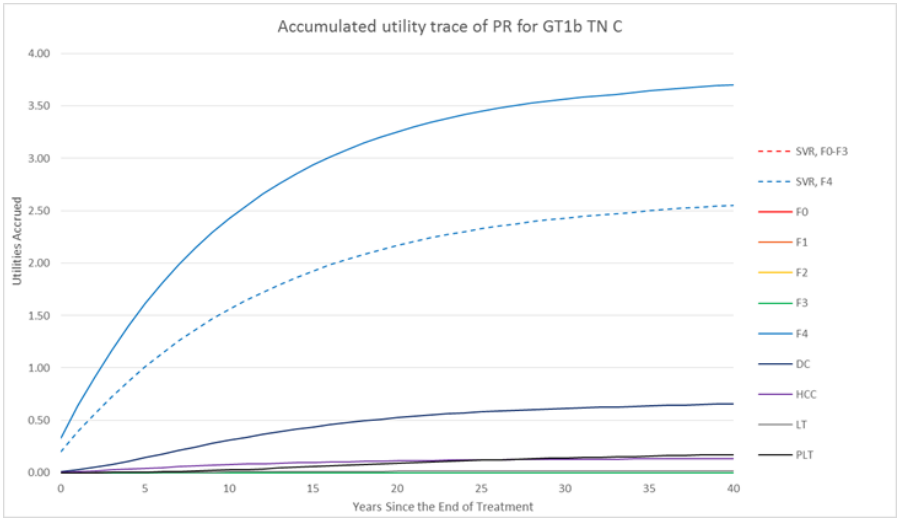
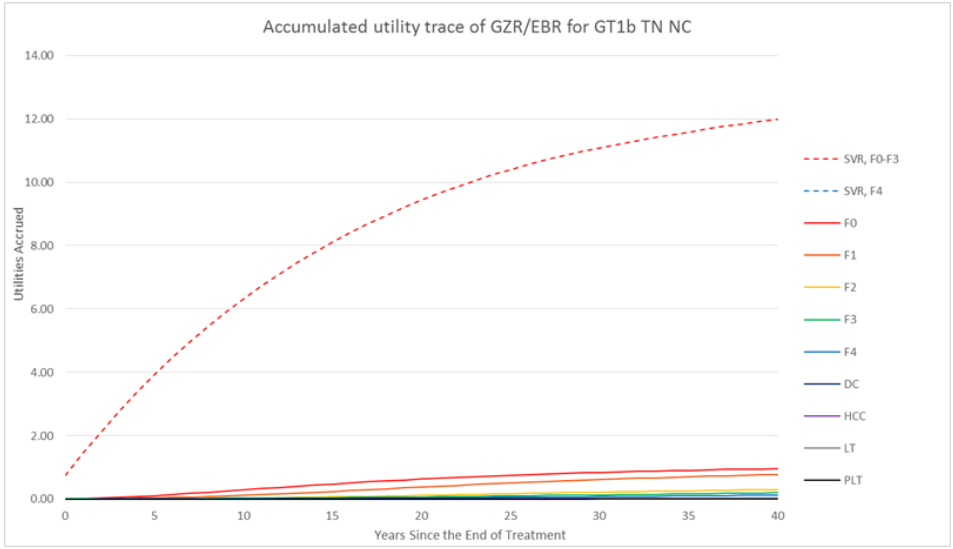


Figure 44. Cumulative QALYs over time – GT1b TN C/NC







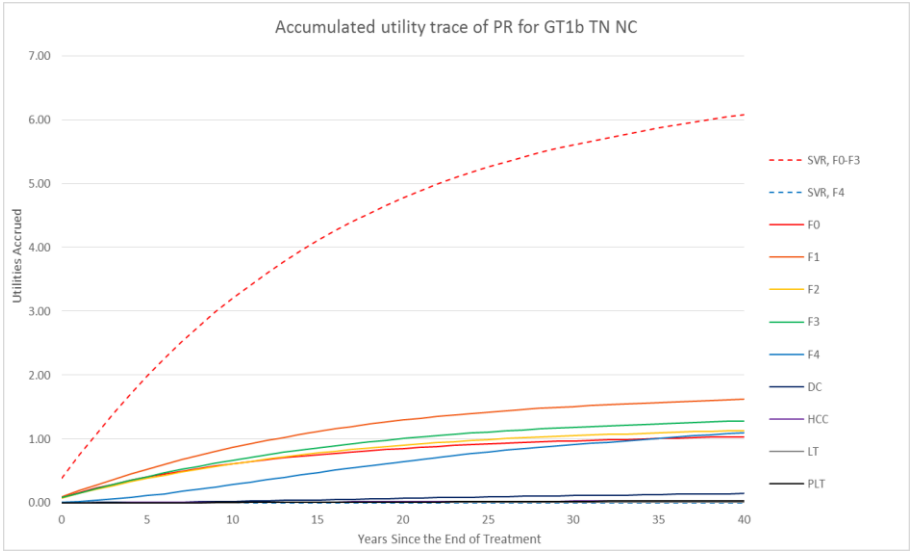
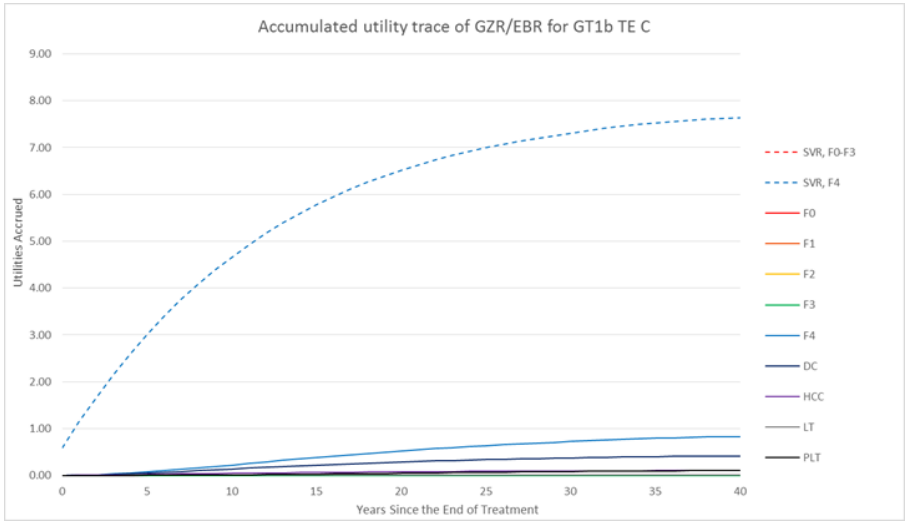
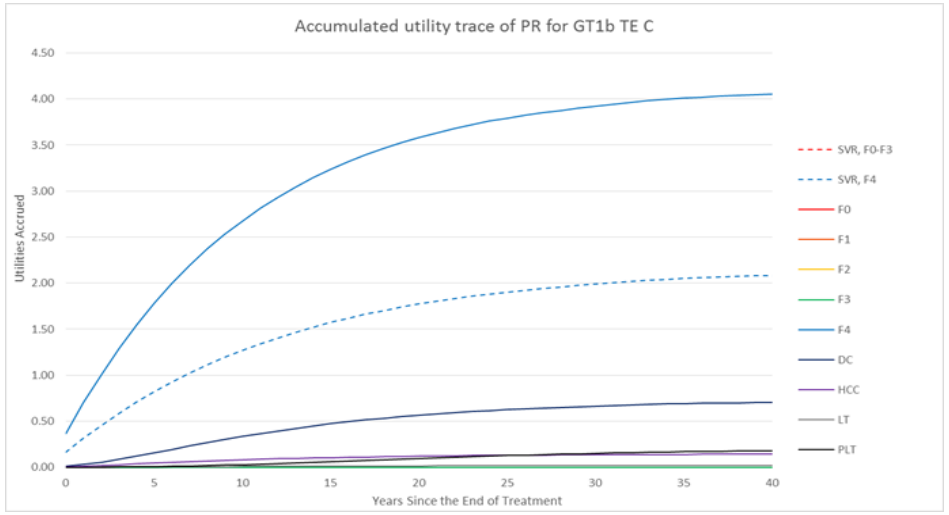
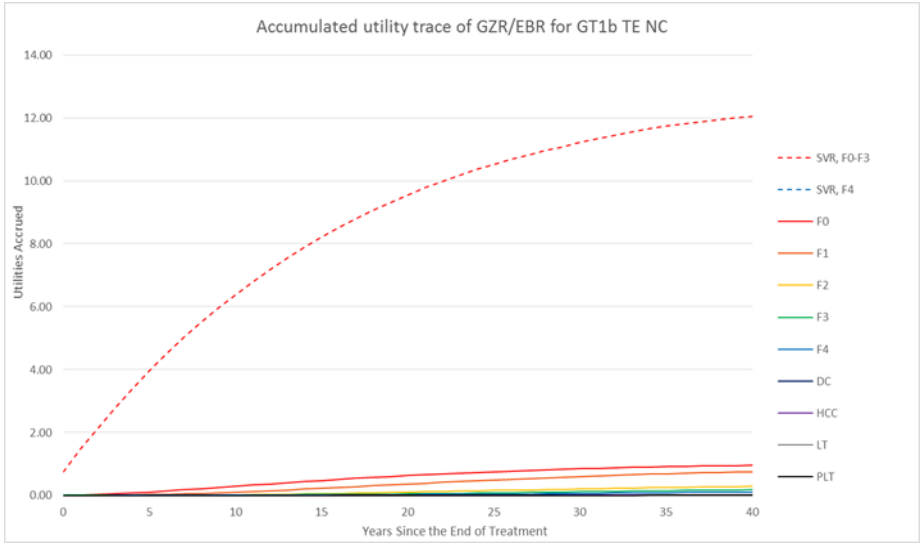


Figure 45. Cumulative QALYs over time – GT1b TE C/NC







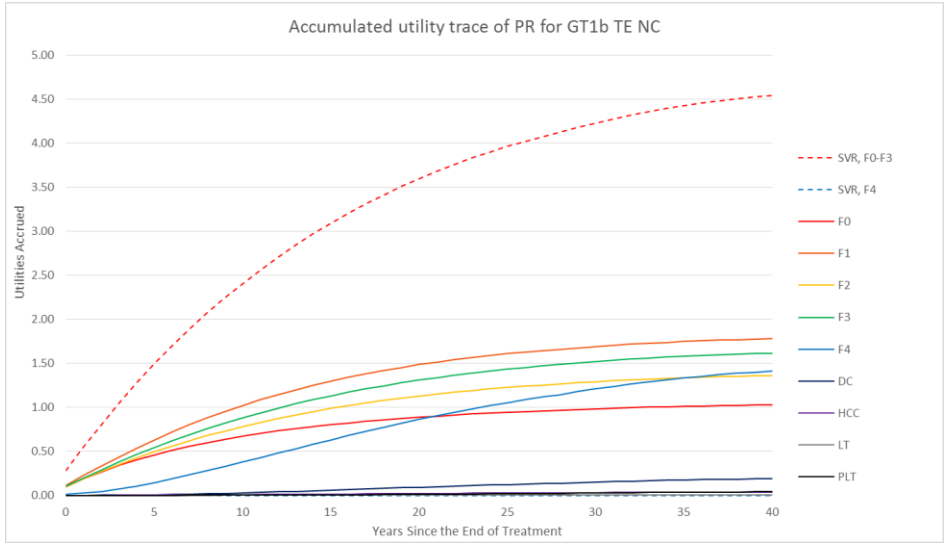
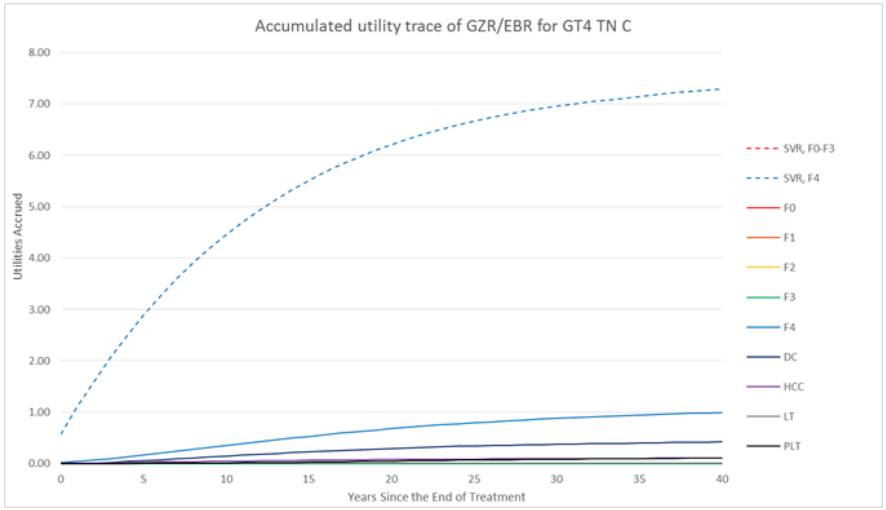
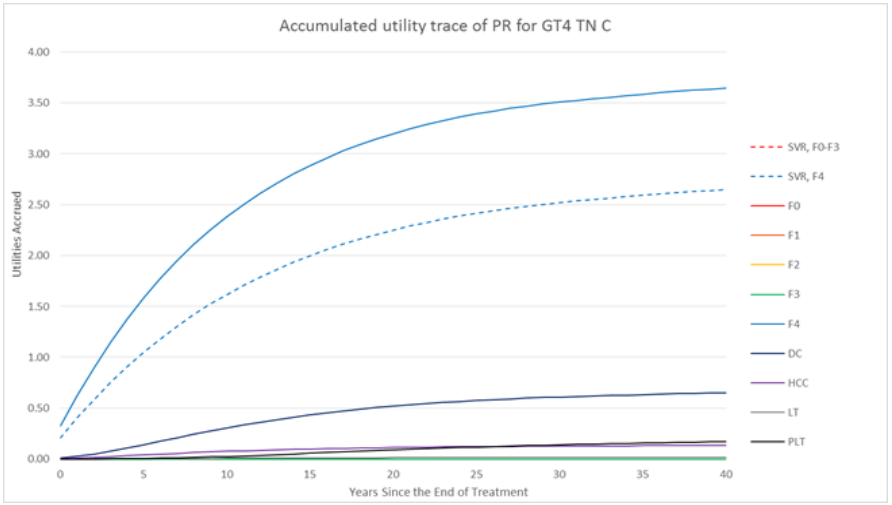
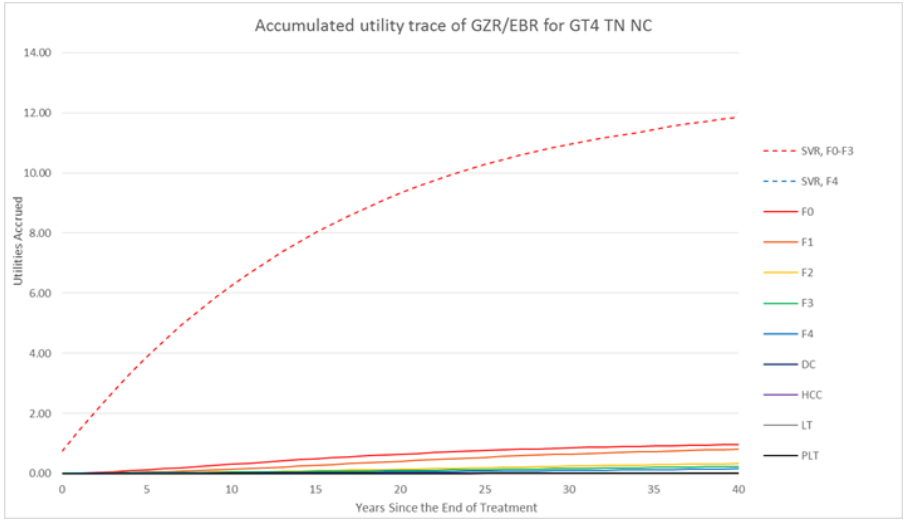


Figure 46. Cumulative QALYs over time – GT4 TN C/NC







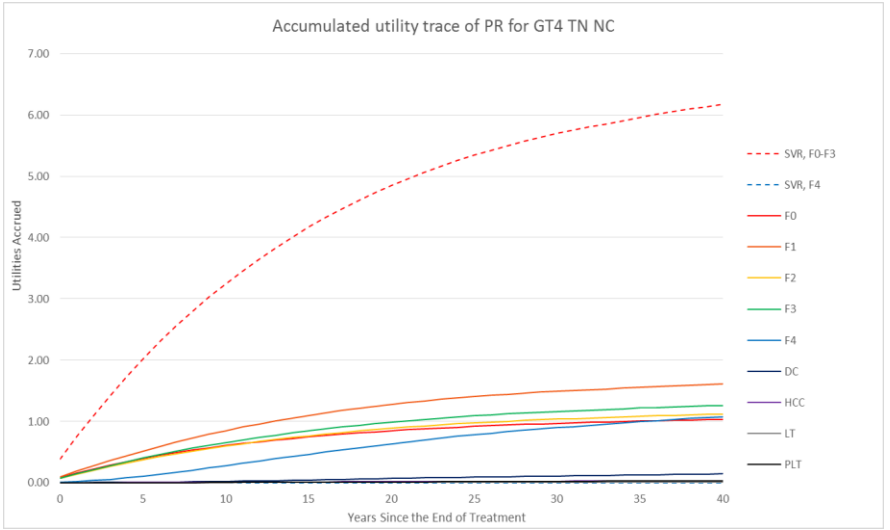
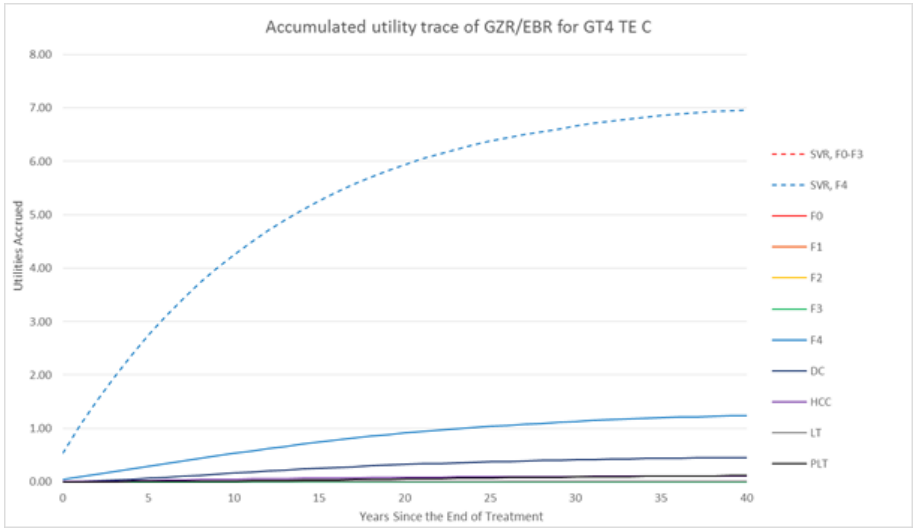
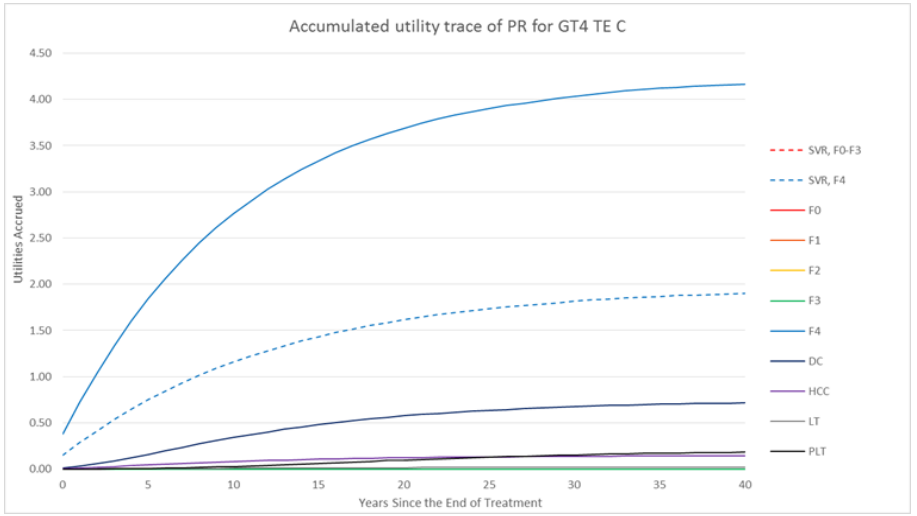
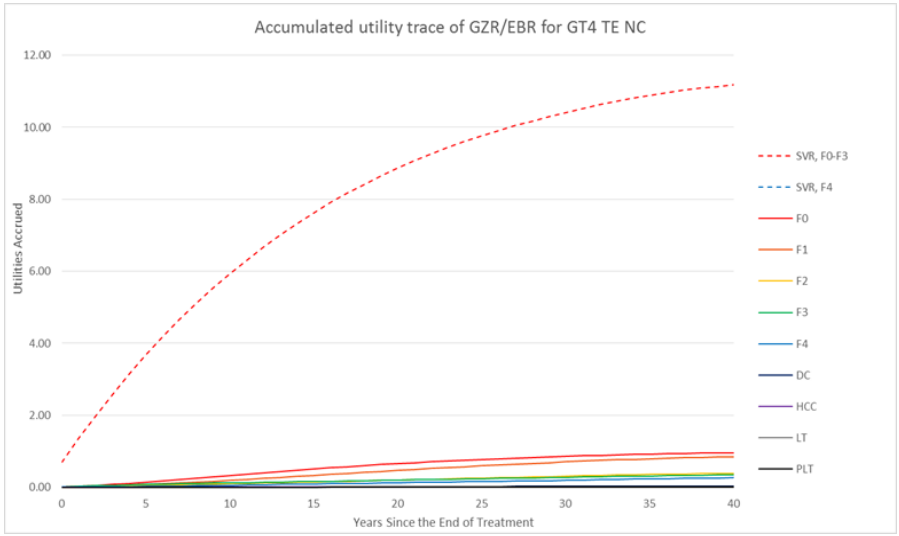
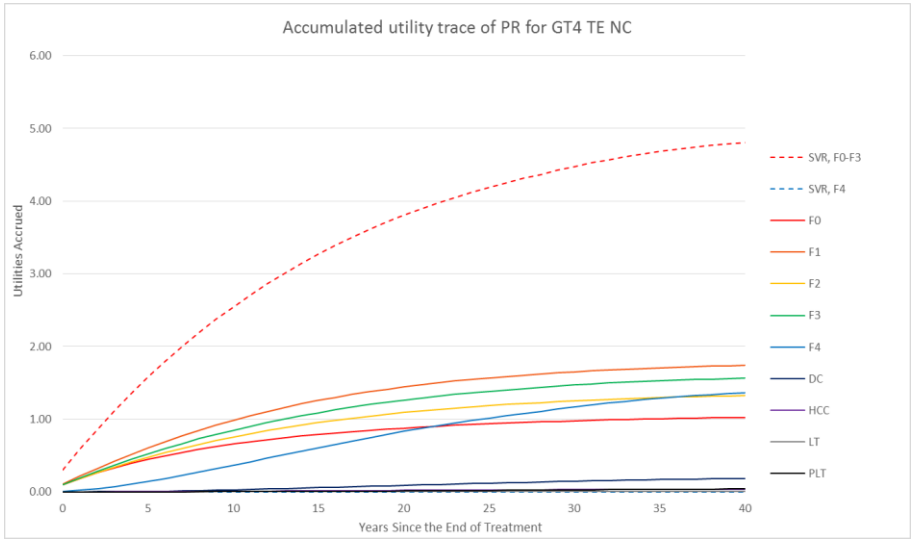


Figure 47. Cumulative QALYs over time – GT4 TE C/NC









5.7.6 Disaggregated results of the base case incremental cost effectiveness analysis

The disaggregated incremental QALYs and costs by grouped health states and predicted resource use are presented below for each subpopulation. Please note that liver disease includes DC and HCC health states.

Table 97. Summary of QALY gain by grouped health states – GT1a TN C

	On treatment			SVR			F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.363			2.693			3.686			0.999		
SOF	0.074	-0.290	5%	6.295	3.603	59%	1.714	-1.973	32%	0.763	-0.237	4%
SMV	0.201	-0.162	4%	4.911	2.218	60%	2.487	-1.199	32%	0.857	-0.142	4%
EBR/GZR	0.126	-0.237	3%	7.416	4.724	60%	1.041	-2.645	33%	0.676	-0.323	4%
LDV/SOF	0.126	-0.237	3%	7.416	4.724	60%	1.041	-2.645	33%	0.676	-0.323	4%
2D/3D	0.226	-0.137	2%	7.086	4.394	60%	1.202	-2.484	34%	0.693	-0.306	4%

Table 98. Summary of QALY gain by grouped health states – GT1a TN NC

	On treatment			SVR			F0-F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.545			6.373			6.324			0.232		
BSC	0.000	-0.545	5%	0.000	-6.373	54%	10.931	4.607	39%	0.473	0.241	2%
LDV/SOF	0.110	-0.435	4%	12.094	5.721	58%	2.852	-3.471	35%	0.042	-0.190	2%
SMV	0.285	-0.260	4%	10.076	3.703	59%	4.081	-2.243	35%	0.109	-0.123	2%
2D/3D	0.164	-0.381	4%	12.432	6.059	58%	2.600	-3.724	36%	0.029	-0.203	2%
EBR/GZR	0.164	-0.380	4%	12.183	5.810	58%	2.765	-3.559	36%	0.038	-0.194	2%
SOF	0.130	-0.415	5%	11.603	5.231	58%	3.150	-3.174	35%	0.058	-0.174	2%
DCV+SOF	0.156	-0.388	4%	12.431	6.059	58%	2.600	-3.724	36%	0.029	-0.203	2%

Table 99. Summary of QALY gain by grouped health states – GT1a TE C

	On treatment			SVR			F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.349			1.700			4.312			1.086		
SMV	0.184	-0.165	3%	5.365	3.665	59%	2.219	-2.093	34%	0.823	-0.262	4%
SOF	0.074	-0.276	5%	5.289	3.589	59%	2.311	-2.001	33%	0.840	-0.246	4%
EBR/GZR	0.126	-0.223	2%	7.022	5.322	59%	1.264	-3.048	34%	0.703	-0.383	4%
LDV/SOF	0.126	-0.223	2%	7.093	5.394	59%	1.222	-3.090	34%	0.698	-0.388	4%
2D/3D	0.226	-0.123	1%	6.978	5.279	60%	1.256	-3.056	35%	0.699	-0.387	4%

Table 100. Summary of QALY gain by grouped health states – GT1a TE NC

	On treatment			SVR			F0-F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.527			4.882			7.118			0.278		
BSC	0.000	-0.527	6%	0.000	-4.882	53%	10.800	3.682	40%	0.471	0.193	2%
SMV	0.267	-0.260	3%	10.032	5.150	58%	3.807	-3.311	37%	0.098	-0.180	2%
2D/3D	0.163	-0.363	3%	11.898	7.016	58%	2.618	-4.501	37%	0.033	-0.245	2%
EBR/GZR	0.164	-0.363	3%	11.422	6.540	58%	2.942	-4.177	37%	0.050	-0.227	2%
LDV/SOF	0.164	-0.363	3%	11.898	7.016	58%	2.618	-4.501	37%	0.033	-0.245	2%
SOF	0.129	-0.397	4%	10.199	5.317	58%	3.775	-3.344	36%	0.095	-0.183	2%
DCV+SOF	0.156	-0.371	3%	11.775	6.893	58%	2.701	-4.417	37%	0.038	-0.240	2%

Table 101. Summary of QALY gain by grouped health states – GT1b TN C

	On treatment			SVR			F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.363			2.595			3.744			1.007		
SOF	0.074	-0.290	4%	7.082	4.487	59%	1.248	-2.496	33%	0.703	-0.304	4%
2D/3D	0.118	-0.245	3%	7.635	5.040	60%	0.915	-2.829	33%	0.660	-0.347	4%
SMV	0.201	-0.162	4%	4.845	2.250	60%	2.526	-1.218	32%	0.862	-0.145	4%
EBR/GZR	0.126	-0.237	3%	7.707	5.112	60%	0.869	-2.875	34%	0.654	-0.353	4%
LDV/SOF	0.126	-0.237	3%	7.631	5.036	60%	0.914	-2.830	33%	0.660	-0.347	4%

Table 102. Summary of QALY gain by grouped health states – GT1b TN NC

	On treatment			SVR			F0-F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.545			6.272			6.390			0.235		
BSC	0.000	-0.545	5%	0.000	-6.272	54%	10.931	4.541	39%	0.473	0.238	2%
LDV/SOF	0.110	-0.435	4%	12.167	5.895	58%	2.804	-3.586	35%	0.039	-0.196	2%
SMV	0.285	-0.260	4%	9.907	3.635	59%	4.192	-2.198	35%	0.115	-0.121	2%
2D/3D	0.165	-0.380	4%	12.503	6.230	58%	2.552	-3.838	36%	0.026	-0.209	2%
EBR/GZR	0.164	-0.380	4%	12.378	6.106	58%	2.635	-3.755	36%	0.031	-0.205	2%
SOF	0.130	-0.415	4%	12.379	6.106	58%	2.636	-3.755	36%	0.031	-0.205	2%
DCV+SOF	0.156	-0.388	4%	12.378	6.106	58%	2.635	-3.755	36%	0.031	-0.205	2%

Table 103. Summary of QALY gain by grouped health states – GT1b TE C

	On treatment			SVR			F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.349			2.100			4.074			1.055		
SMV	0.184	-0.165	2%	6.026	3.926	59%	1.824	-2.250	34%	0.772	-0.283	4%
2D/3D	0.118	-0.231	3%	7.558	5.458	59%	0.947	-3.127	34%	0.662	-0.392	4%
EBR/GZR	0.126	-0.223	2%	7.705	5.605	59%	0.856	-3.218	34%	0.650	-0.405	4%
SOF	0.074	-0.276	6%	4.824	2.724	58%	2.590	-1.484	32%	0.876	-0.179	4%
LDV/SOF	0.126	-0.223	2%	7.705	5.606	59%	0.856	-3.218	34%	0.650	-0.405	4%

Table 104. Summary of QALY gain by grouped health states – GT1b TE NC

	On treatment			SVR			F0-F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.527			4.616			7.299			0.288		
BSC	0.000	-0.527	6%	0.000	-4.616	52%	10.800	3.501	40%	0.471	0.183	2%
SMV	0.267	-0.260	3%	9.941	5.325	58%	3.869	-3.430	37%	0.101	-0.187	2%
2D/3D	0.164	-0.363	3%	12.328	7.712	58%	2.325	-4.975	37%	0.017	-0.270	2%
EBR/GZR	0.164	-0.363	3%	12.220	7.604	58%	2.399	-4.901	37%	0.021	-0.266	2%
LDV/SOF	0.164	-0.363	3%	12.220	7.604	58%	2.399	-4.901	37%	0.021	-0.266	2%
SOF	0.129	-0.397	4%	10.535	5.919	58%	3.546	-3.753	37%	0.083	-0.205	2%
DCV+SOF	0.156	-0.371	6%	12.220	7.604	52%	2.399	-4.901	40%	0.021	-0.266	2%

Table 105. Summary of QALY gain by grouped health states – GT4 TN C

	On treatment			SVR			F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.363			2.693			3.686			0.999		
SOF	0.074	-0.290	4%	6.815	4.122	59%	1.406	-2.280	33%	0.724	-0.276	4%
SMV	0.201	-0.162	4%	4.911	2.218	60%	2.487	-1.199	32%	0.857	-0.142	4%
EBR/GZR	0.126	-0.237	3%	7.416	4.724	60%	1.041	-2.645	33%	0.676	-0.323	4%
LDV/SOF	0.126	-0.237	3%	7.416	4.724	60%	1.041	-2.645	33%	0.676	-0.323	4%
DCV/PR	0.190	-0.173	2%	7.508	4.815	60%	0.944	-2.742	34%	0.659	-0.340	4%
2D/3D	0.235	-0.128	2%	7.293	4.600	60%	1.077	-2.609	34%	0.677	-0.323	4%

Table 106. Summary of QALY gain by grouped health states – GT4 TN NC

	On treatment			SVR			F0-F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.545			6.373			6.324			0.232		
BSC	0.000	-0.545	5%	0.000	-6.373	54%	10.931	4.607	39%	0.473	0.241	2%
SMV	0.285	-0.260	4%	10.076	3.703	59%	4.081	-2.243	35%	0.109	-0.123	2%
2D/3D	0.165	-0.380	4%	12.431	6.059	58%	2.600	-3.724	36%	0.029	-0.203	2%
EBR/GZR	0.164	-0.380	4%	12.183	5.810	58%	2.765	-3.559	36%	0.038	-0.194	2%
DCV/PR	0.266	-0.279	3%	12.333	5.961	59%	2.579	-3.744	37%	0.029	-0.203	2%

Table 107. Summary of QALY gain by grouped health states – GT4 TE C

	On treatment			SVR			F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.349			1.914			4.185			1.069		
SMV	0.184	-0.165	3%	5.492	3.578	59%	2.143	-2.041	34%	0.814	-0.256	4%
SOF	0.074	-0.276	5%	5.289	3.375	59%	2.311	-1.874	33%	0.840	-0.229	4%
EBR/GZR	0.126	-0.223	3%	7.022	5.109	59%	1.264	-2.920	34%	0.703	-0.366	4%
LDV/SOF	0.126	-0.223	3%	7.093	5.180	59%	1.222	-2.963	34%	0.698	-0.371	4%
DCV/PR	0.190	-0.159	2%	7.182	5.269	59%	1.125	-3.059	34%	0.681	-0.388	4%
2D/3D	0.235	-0.114	1%	6.975	5.061	60%	1.256	-2.929	35%	0.698	-0.371	4%

Table 108. Summary of QALY gain by grouped health states – GT4 TE NC

	On treatment			SVR			F0-F4			Liver disease and transplant		
	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment	QALYs	Increment	% abs. increment
PR	0.527			4.882			7.118			0.278		
BSC	0.000	-0.527	6%	0.000	-4.882	53%	10.800	3.682	40%	0.471	0.193	2%
SMV	0.267	-0.260	3%	10.032	5.150	58%	3.807	-3.311	37%	0.098	-0.180	2%
2D/3D	0.164	-0.363	3%	11.898	7.016	58%	2.618	-4.501	37%	0.033	-0.245	2%
EBR/GZR	0.164	-0.363	3%	11.422	6.540	58%	2.942	-4.177	37%	0.050	-0.227	2%
LDV/SOF	0.164	-0.363	3%	11.898	7.016	58%	2.618	-4.501	37%	0.033	-0.245	2%
DCV/PR	0.265	-0.262	2%	11.682	6.800	58%	2.680	-4.439	38%	0.037	-0.241	2%
DCV+SOF	0.156	-0.371	3%	11.775	6.893	58%	2.701	-4.417	37%	0.038	-0.240	2%

Table 109. Summary of costs by grouped health states – GT1a TN C

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,283			£5,113			£968			£42,236		
SOF	£29,023	£22,740	65%	£2,465	-£2,648	8%	£447	-£521	1%	£32,973	-£9,263	26%
SMV	£24,094	£17,812	72%	£3,741	-£1,372	6%	£993	£26	0%	£36,552	-£5,684	23%
EBR/GZR	£36,423	£30,141	65%	£2,465	-£2,648	6%	£26	-£941	2%	£29,641	-£12,594	27%
LDV/SOF	£38,790	£32,507	67%	£2,465	-£2,648	5%	£44	-£923	2%	£29,642	-£12,594	26%
2D/3D	£62,999	£56,716	80%	£2,714	-£2,399	3%	£776	-£192	0%	£30,277	-£11,959	17%

Table 110. Summary of costs by grouped health states – GT1a TN NC

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,844			£3,750			£385			£15,600		
BSC	£0	-£6,844	26%	£0	-£3,750	14%	£0	-£385	1%	£30,513	£14,912	58%
LDV/SOF	£25,975	£19,131	58%	£2,143	-£1,607	5%	£7	-£378	1%	£3,933	-£11,667	36%
SMV	£25,260	£18,416	69%	£3,037	-£713	3%	£362	-£23	0%	£8,034	-£7,567	28%
2D/3D	£35,040	£28,195	66%	£2,268	-£1,482	3%	£55	-£330	1%	£3,116	-£12,484	29%
EBR/GZR	£36,445	£29,601	68%	£2,268	-£1,482	3%	£16	-£369	1%	£3,659	-£11,941	28%
SOF	£36,370	£29,526	71%	£2,268	-£1,482	4%	£290	-£96	0%	£4,927	-£10,673	26%
DCV+SOF	£59,422	£52,578	79%	£2,268	-£1,482	2%	£95	-£290	0%	£3,116	-£12,484	19%

Table 111. Summary of costs by grouped health states – GT1a TE C

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,283			£4,275			£968			£43,650		
SMV	£24,094	£17,812	61%	£2,902	-£1,372	5%	£993	£26	0%	£33,689	-£9,961	34%
SOF	£29,023	£22,740	65%	£1,626	-£2,648	8%	£447	-£521	1%	£34,330	-£9,319	26%
EBR/GZR	£36,423	£30,141	63%	£1,626	-£2,648	5%	£26	-£941	2%	£29,212	-£14,438	30%
LDV/SOF	£38,790	£32,507	64%	£1,626	-£2,648	5%	£44	-£923	2%	£29,006	-£14,643	29%
2D/3D	£62,999	£56,716	77%	£1,875	-£2,399	3%	£776	-£192	0%	£29,029	-£14,621	20%

Table 112. Summary of costs by grouped health states – GT1a TE NC

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,844			£3,107			£385			£17,499		
BSC	£0	-£6,844	32%	£0	-£3,107	14%	£0	-£385	2%	£28,835	£11,336	52%
SMV	£25,260	£18,416	62%	£2,394	-£713	2%	£362	-£23	0%	£6,965	-£10,534	35%
2D/3D	£35,040	£28,195	64%	£1,625	-£1,482	3%	£55	-£330	1%	£3,195	-£14,304	32%
EBR/GZR	£36,445	£29,601	66%	£1,625	-£1,482	3%	£16	-£369	1%	£4,211	-£13,288	30%
LDV/SOF	£38,916	£32,072	66%	£1,625	-£1,482	3%	£12	-£374	1%	£3,195	-£14,304	30%
SOF	£36,370	£29,526	71%	£1,625	-£1,482	4%	£290	-£96	0%	£6,826	-£10,673	26%
DCV+SOF	£59,422	£52,578	77%	£1,625	-£1,482	2%	£95	-£290	0%	£3,457	-£14,042	21%

Table 113. Summary of costs by grouped health states – GT1b TN C

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,283			£5,113			£968			£42,521		
SOF	£29,023	£22,740	60%	£2,465	-£2,648	7%	£447	-£521	1%	£30,693	-£11,828	31%
2D/3D	£32,731	£26,449	62%	£2,465	-£2,648	6%	£714	-£253	1%	£29,036	-£13,485	31%
SMV	£24,094	£17,812	71%	£3,741	-£1,372	5%	£993	£26	0%	£36,743	-£5,778	23%
EBR/GZR	£36,423	£30,141	64%	£2,465	-£2,648	6%	£26	-£941	2%	£28,800	-£13,721	29%
LDV/SOF	£38,790	£32,507	66%	£2,465	-£2,648	5%	£44	-£923	2%	£29,021	-£13,500	27%

Table 114. Summary of costs by grouped health states – GT1b TN NC

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,844			£3,750			£385			£15,820		
BSC	£0	-£6,844	27%	£0	-£3,750	15%	£0	-£385	2%	£30,513	£14,692	57%
LDV/SOF	£25,975	£19,131	58%	£2,143	-£1,607	5%	£7	-£378	1%	£3,773	-£12,047	36%
SMV	£25,260	£18,416	69%	£3,037	-£713	3%	£362	-£23	0%	£8,402	-£7,418	28%
2D/3D	£34,982	£28,137	66%	£2,268	-£1,482	3%	£22	-£363	1%	£2,960	-£12,861	30%
EBR/GZR	£36,445	£29,601	67%	£2,268	-£1,482	3%	£16	-£369	1%	£3,233	-£12,587	29%
SOF	£36,370	£29,526	68%	£2,268	-£1,482	3%	£290	-£96	0%	£3,233	-£12,587	29%
DCV+SOF	£59,422	£52,578	79%	£2,268	-£1,482	2%	£95	-£290	0%	£3,233	-£12,587	19%

Table 115. Summary of costs by grouped health states – GT1b TE C

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,283			£4,275			£968			£42,483		
SMV	£24,094	£17,812	60%	£2,902	-£1,372	5%	£993	£26	0%	£31,770	-£10,714	36%
2D/3D	£32,731	£26,449	60%	£1,626	-£2,648	6%	£714	-£253	1%	£27,682	-£14,801	34%
EBR/GZR	£36,423	£30,141	62%	£1,626	-£2,648	5%	£26	-£941	2%	£27,228	-£15,255	31%
SOF	£29,023	£22,740	70%	£1,626	-£2,648	8%	£447	-£521	2%	£35,682	-£6,802	21%
LDV/SOF	£38,790	£32,507	63%	£1,626	-£2,648	5%	£44	-£923	2%	£27,229	-£15,254	30%

Table 116. Summary of costs by grouped health states – GT1b TE NC

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,844			£3,107			£385			£18,070		
BSC	£0	-£6,844	32%	£0	-£3,107	15%	£0	-£385	2%	£28,835	£10,765	51%
SMV	£25,260	£18,416	61%	£2,394	-£713	2%	£362	-£23	0%	£7,160	-£10,910	36%
2D/3D	£34,982	£28,137	61%	£1,625	-£1,482	3%	£22	-£363	1%	£2,276	-£15,794	35%
EBR/GZR	£36,445	£29,601	63%	£1,625	-£1,482	3%	£16	-£369	1%	£2,508	-£15,562	33%
LDV/SOF	£38,916	£32,072	65%	£1,625	-£1,482	3%	£12	-£374	1%	£2,508	-£15,562	31%
SOF	£36,370	£29,526	69%	£1,625	-£1,482	3%	£290	-£96	0%	£6,108	-£11,961	28%
DCV+SOF	£59,422	£52,578	75%	£1,625	-£1,482	2%	£95	-£290	0%	£2,508	-£15,562	22%

Table 117. Summary of costs by grouped health states – GT4 TN C

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,283			£5,113			£968			£42,236		
SOF	£29,023	£22,740	62%	£2,465	-£2,648	7%	£447	-£521	1%	£31,467	-£10,769	29%
SMV	£24,094	£17,812	72%	£3,741	-£1,372	6%	£993	£26	0%	£36,552	-£5,684	23%
EBR/GZR	£36,423	£30,141	65%	£2,465	-£2,648	6%	£26	-£941	2%	£29,641	-£12,594	27%
LDV/SOF	£38,790	£32,507	67%	£2,465	-£2,648	5%	£44	-£923	2%	£29,642	-£12,594	26%
DCV/PR	£52,449	£46,166	74%	£2,714	-£2,399	4%	£214	-£753	1%	£28,973	-£13,263	21%
2D/3D	£60,255	£53,972	78%	£2,714	-£2,399	3%	£714	-£253	0%	£29,651	-£12,585	18%

Table 118. Summary of costs by grouped health states – GT4 TN NC

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,844			£3,750			£385			£15,600		
BSC	£0	-£6,844	26%	£0	-£3,750	14%	£0	-£385	1%	£30,513	£14,912	58%
SMV	£25,260	£18,416	69%	£3,037	-£713	3%	£362	-£23	0%	£8,034	-£7,567	28%
2D/3D	£32,378	£25,534	64%	£2,268	-£1,482	4%	£22	-£363	1%	£3,116	-£12,484	31%
EBR/GZR	£36,445	£29,601	68%	£2,268	-£1,482	3%	£16	-£369	1%	£3,659	-£11,941	28%
DCV/PR	£52,476	£45,632	76%	£2,516	-£1,234	2%	£95	-£290	0%	£3,091	-£12,509	21%

Table 119. Summary of costs by grouped health states – GT4 TE C

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,283			£4,275			£968			£43,026		
SMV	£24,094	£17,812	62%	£2,902	-£1,372	5%	£993	£26	0%	£33,321	-£9,705	34%
SOF	£29,023	£22,740	66%	£1,626	-£2,648	8%	£447	-£521	2%	£34,330	-£8,696	25%
EBR/GZR	£36,423	£30,141	63%	£1,626	-£2,648	6%	£26	-£941	2%	£29,212	-£13,815	29%
LDV/SOF	£38,790	£32,507	65%	£1,626	-£2,648	5%	£44	-£923	2%	£29,006	-£14,020	28%
DCV/PR	£52,449	£46,166	72%	£1,875	-£2,399	4%	£214	-£753	1%	£28,355	-£14,671	23%
2D/3D	£60,255	£53,972	76%	£1,875	-£2,399	3%	£714	-£253	0%	£29,013	-£14,013	20%

Table 120. Summary of costs by grouped health states – GT4 TE NC

	Treatment			Monitoring			AE			Health states		
	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment	Costs	Increment	% abs. increment
PR	£6,844			£3,107			£385			£17,499		
BSC	£0	-£6,844	32%	£0	-£3,107	14%	£0	-£385	2%	£28,835	£11,336	52%
SMV	£25,260	£18,416	62%	£2,394	-£713	2%	£362	-£23	0%	£6,965	-£10,534	35%
2D/3D	£32,378	£25,534	61%	£1,625	-£1,482	4%	£22	-£363	1%	£3,195	-£14,304	34%
EBR/GZR	£36,445	£29,601	66%	£1,625	-£1,482	3%	£16	-£369	1%	£4,211	-£13,288	30%
LDV/SOF	£38,916	£32,072	66%	£1,625	-£1,482	3%	£12	-£374	1%	£3,195	-£14,304	30%
DCV/PR	£52,476	£45,632	75%	£1,873	-£1,234	2%	£95	-£290	0%	£3,429	-£14,070	23%
DCV+SOF	£59,422	£52,578	77%	£1,625	-£1,482	2%	£95	-£290	0%	£3,457	-£14,042	21%

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix 18.

The probabilistic sensitivity results confirm the robustness of the results presented in section 5.7. It is of note that the variation on PSA results of specific regimens, i.e. SOF and SMV, can be attributed to the wide confidence intervals of the NMA results due to the small sample size in specific subgroups.

- **GT1a TN C**

Table 121. Probabilistic sensitivity analysis results – GT1a TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£54,439	7.768	-	-	-
SMV	£63,871	8.516	£9,432	0.748	£12,604
SOF	£68,033	8.723	£13,595	0.956	£14,228
EBR/GZR	£68,852	9.271	£14,413	1.503	£9,587
LDV/SOF	£70,587	9.264	£16,148	1.497	£10,791
2D/3D	£96,377	9.170	£41,938	1.403	£29,900

Figure 48. Scatterplot of PSA results (1,000 simulations) – GT1a TN C

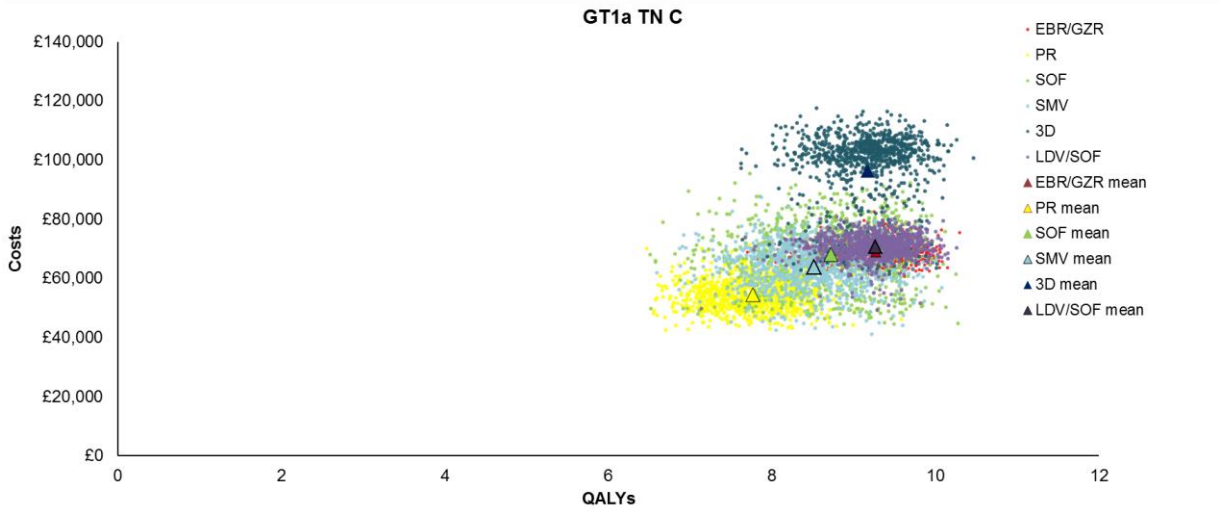
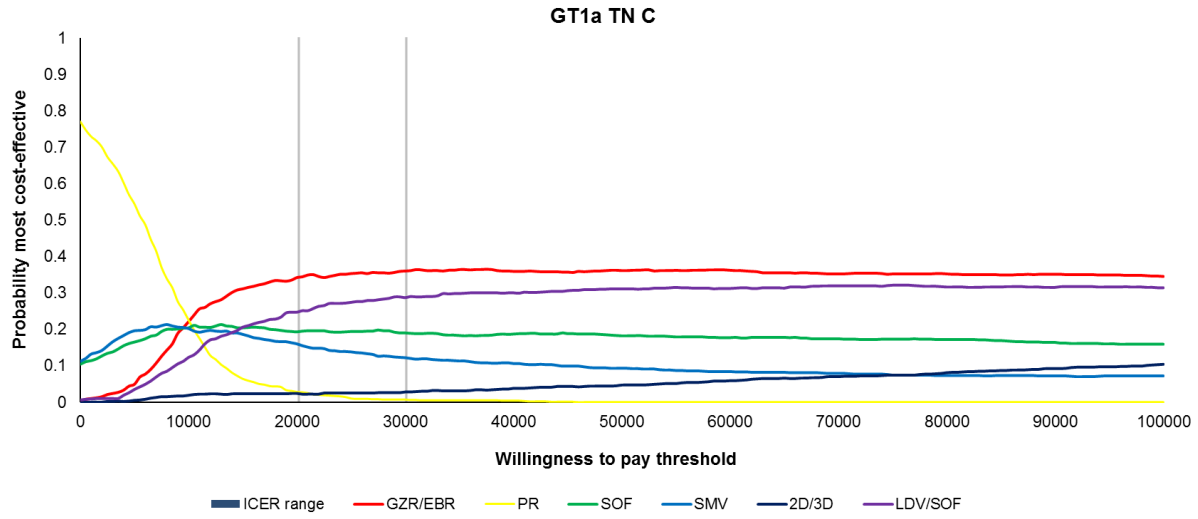


Figure 49. Cost-effectiveness acceptability curve – GT1a TN C



- **GT1a TN NC**

Table 122. Probabilistic sensitivity analysis results – GT1a TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 26,627	13.477	-	-	-
BSC	£ 30,406	11.415	£ 3,779	-2.063	Dominated
LDV/SOF	£ 32,259	15.084	£ 5,632	1.606	£3,507
SMV	£ 35,537	14.550	£ 8,910	1.072	£8,311
2D/3D	£ 40,469	15.211	£ 13,842	1.734	£7,983
EBR/GZR	£ 42,335	15.154	£ 15,708	1.677	£9,367
SOF	£ 43,654	14.896	£ 17,027	1.418	£12,005
DCV+SOF	£ 64,903	15.169	£ 38,277	1.691	£22,629

Figure 50. Scatterplot of PSA results (1,000 simulations) – GT1a TN NC

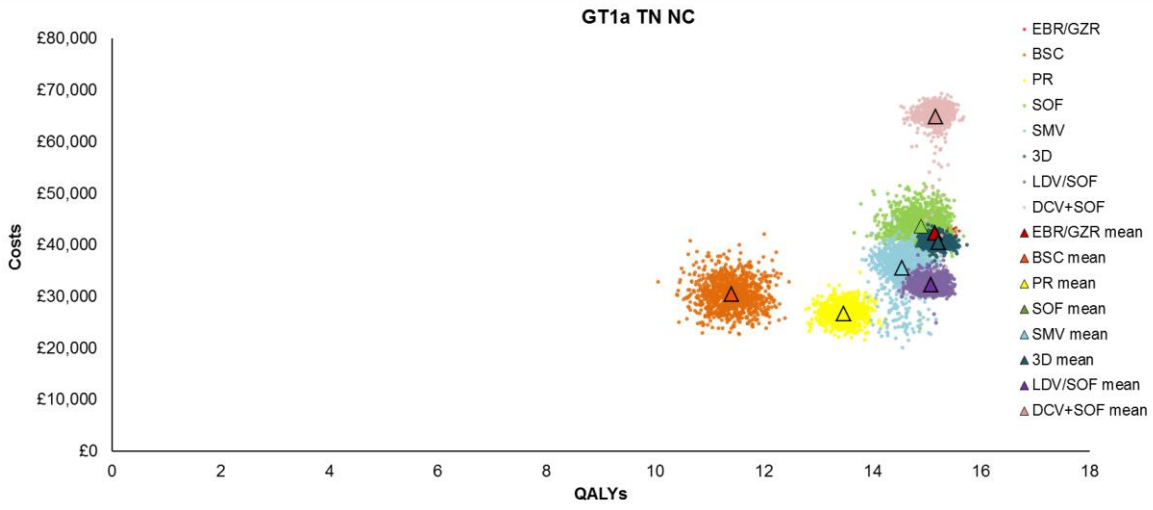
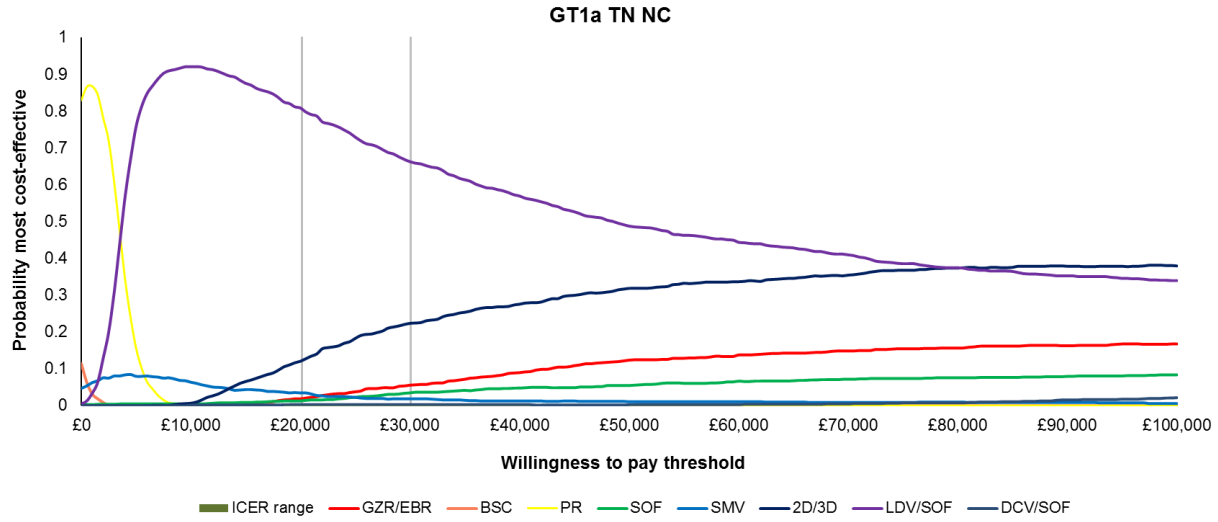


Figure 51. Cost-effectiveness acceptability curve – GT1a TN NC



- **GT1a TE C**

Table 123. Probabilistic sensitivity analysis results – GT1a TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 54,596	7.467	-	-	-
SMV	£ 61,805	8.525	£ 7,208	1.058	£6,814
EBR/GZR	£ 67,223	9.123	£ 12,627	1.656	£7,625
SOF	£ 68,552	8.433	£ 13,956	0.966	£14,440
LDV/SOF	£ 69,633	9.068	£ 15,037	1.601	£9,394
2D/3D	£ 95,656	9.004	£ 41,060	1.537	£26,718

Figure 52. Scatterplot of PSA results (1,000 simulations) – GT1a TE C

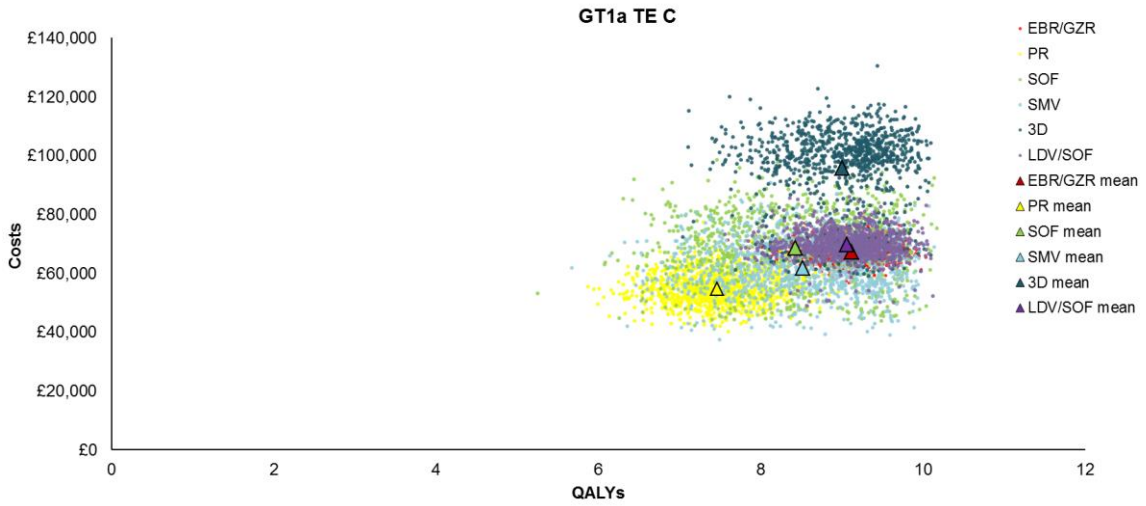
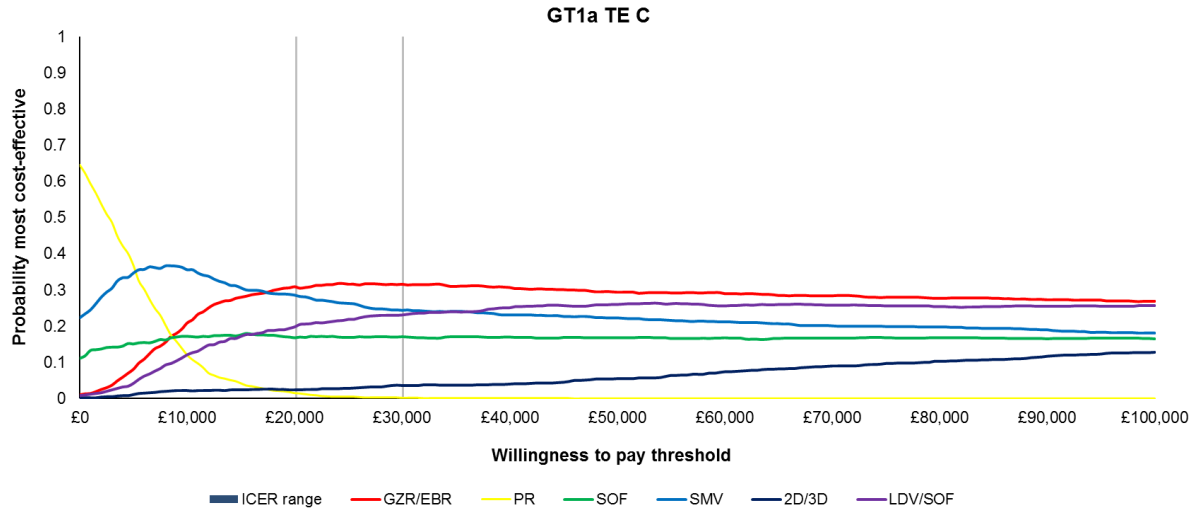


Figure 53. Cost-effectiveness acceptability curve – GT1a TE C



- **GT1a TE NC**

Table 124. Probabilistic sensitivity analysis results – GT1a TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 27,674	12.816	-	-	-
BSC	£ 28,899	11.280	£ 1,225	-1.536	Dominated
SMV	£ 34,540	14.177	£ 6,866	1.361	£5,045
2D/3D	£ 40,329	14.645	£ 12,655	1.829	£6,919
EBR/GZR	£ 42,265	14.582	£ 14,592	1.766	£8,264
LDV/SOF	£ 44,130	14.661	£ 16,456	1.845	£8,919
SOF	£ 44,907	14.190	£ 17,233	1.374	£12,541
DCV+SOF	£ 65,099	14.552	£ 37,426	1.736	£21,554

Figure 54. Scatterplot of PSA results (1,000 simulations) – GT1a TE NC

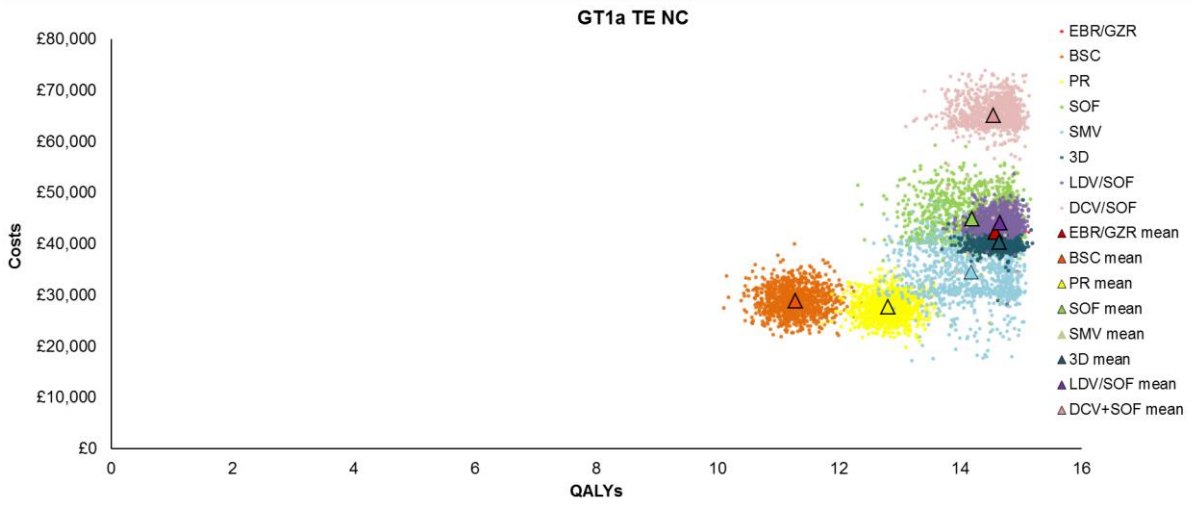
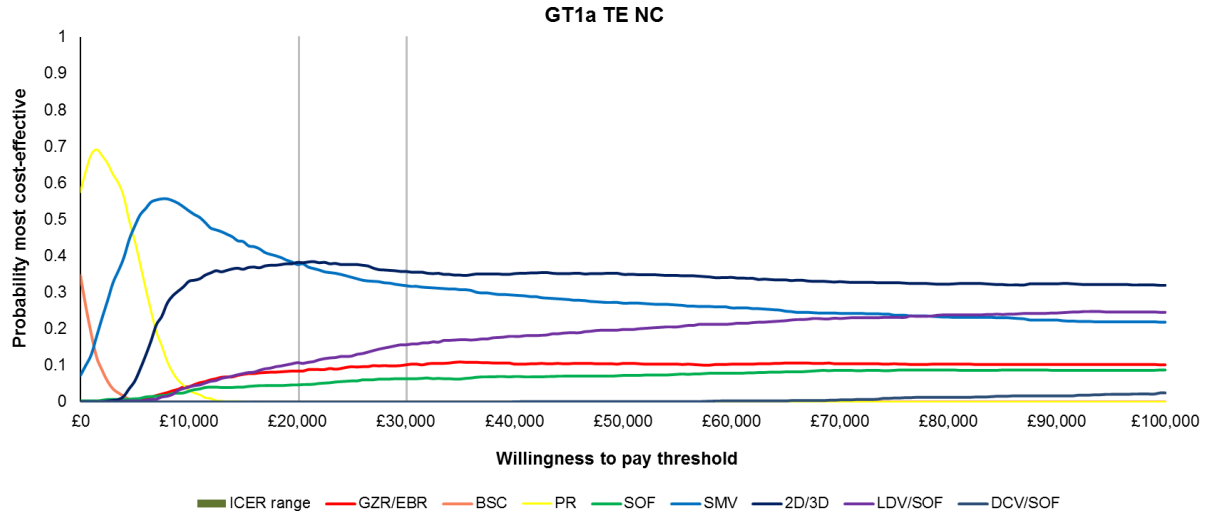


Figure 55. Cost-effectiveness acceptability curve – GT1a TE NC



- **GT1b TN C**

Table 125. Probabilistic sensitivity analysis results – GT1b TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 54,586	7.756	-	-	-
SMV	£ 64,438	8.504	£ 9,853	0.748	£13,170
2D/3D	£ 64,550	9.262	£ 9,964	1.506	£6,615
SOF	£ 66,361	8.926	£ 11,775	1.170	£10,064
EBR/GZR	£ 67,726	9.388	£ 13,140	1.632	£8,051
LDV/SOF	£ 70,406	9.328	£ 15,821	1.572	£10,062

Figure 56. Scatterplot of PSA results (1,000 simulations) – GT1b TN C

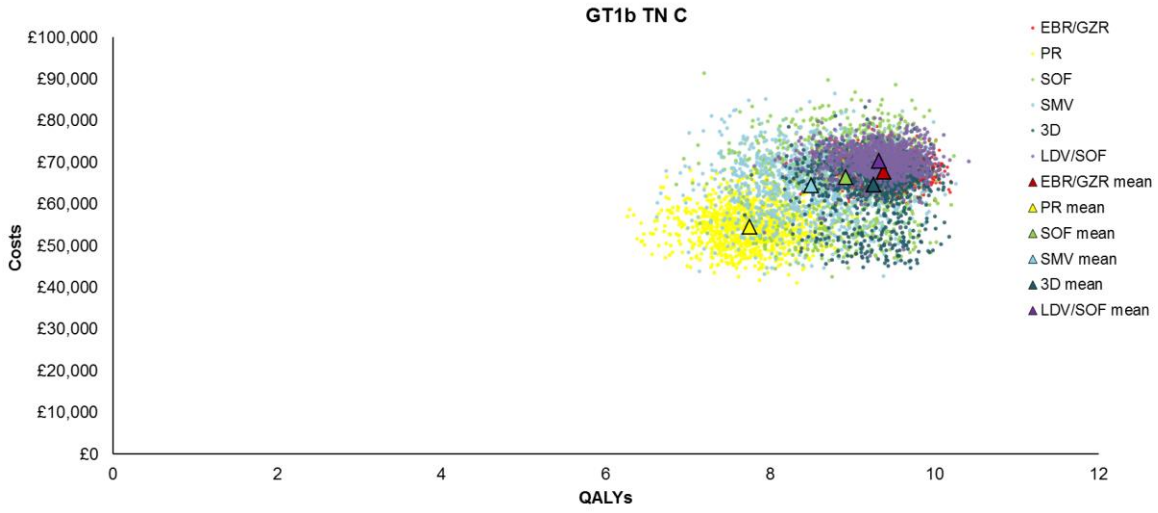
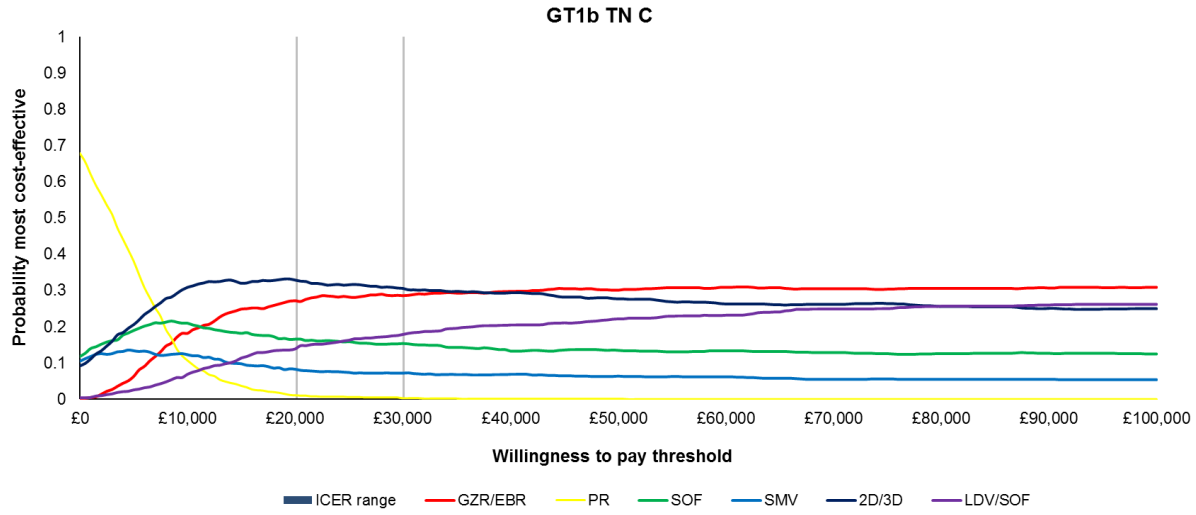


Figure 57. Cost-effectiveness acceptability curve – GT1b TN C



- **GT1b TN NC**

Table 126. Probabilistic sensitivity analysis results – GT1b TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 26,798	13.458	-	-	-
BSC	£ 30,326	11.421	£ 3,528	-2.037	Dominated
LDV/SOF	£ 32,196	15.074	£ 5,399	1.616	£3,340
SMV	£ 35,982	14.500	£ 9,184	1.043	£8,808
2D/3D	£ 40,292	15.237	£ 13,495	1.779	£7,585
SOF	£ 41,963	15.159	£ 15,165	1.702	£8,912
EBR/GZR	£ 41,940	15.216	£ 15,142	1.759	£8,609
DCV+SOF	£ 65,425	15.076	£ 38,628	1.619	£23,860

Figure 58. Scatterplot of PSA results (1,000 simulations) – GT1b TN NC

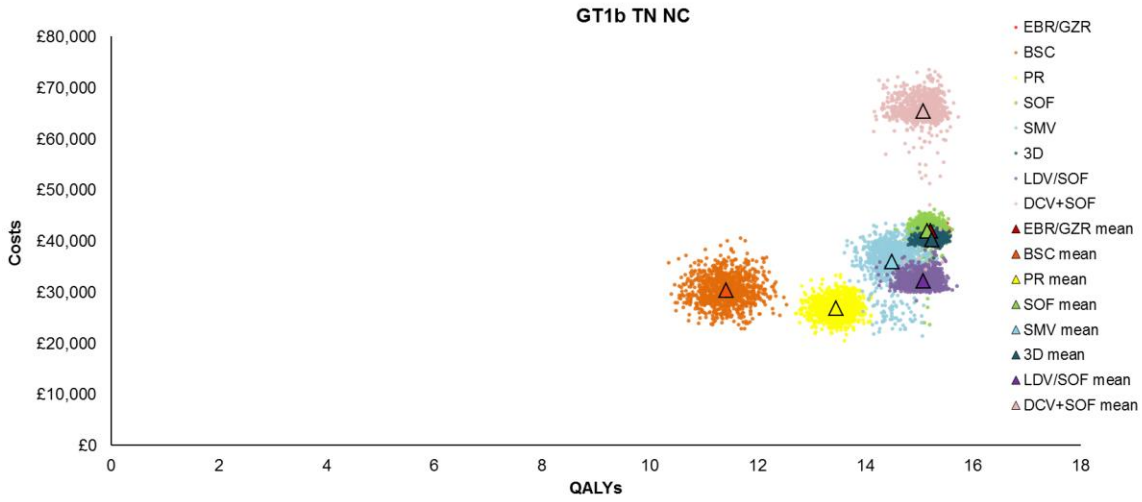
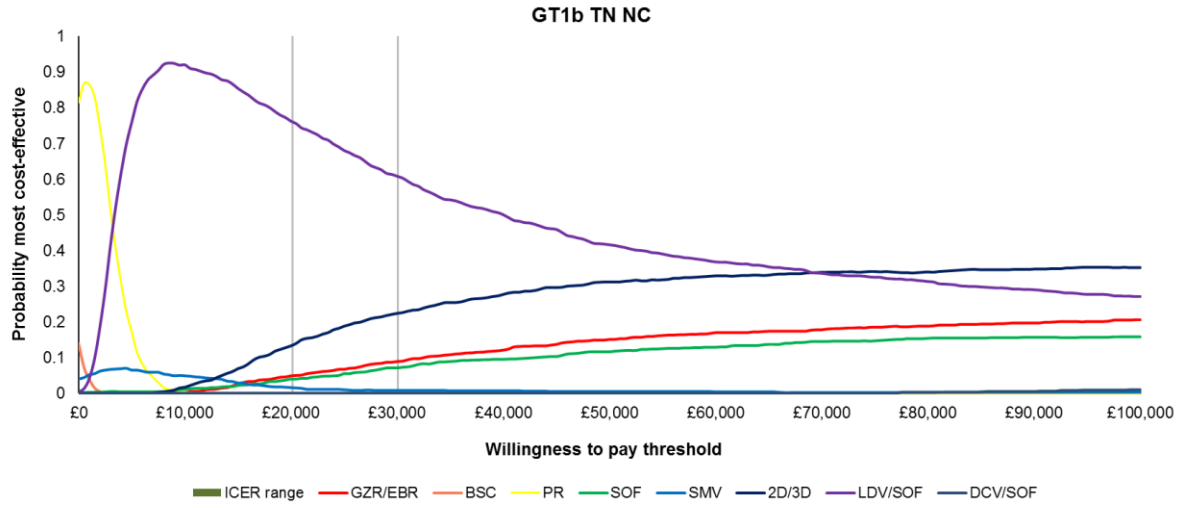


Figure 59. Cost-effectiveness acceptability curve – GT1b TN NC



- **GT1b TE C**

Table 127. Probabilistic sensitivity analysis results – GT1b TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 53,777	7.646	-	-	-
SMV	£ 60,820	8.641	£ 7,043	0.996	£7,074
2D/3D	£ 64,381	8.970	£ 10,605	1.324	£8,010
EBR/GZR	£ 65,235	9.365	£ 11,459	1.719	£6,667
LDV/SOF	£ 68,304	9.229	£ 14,528	1.583	£9,175
SOF	£ 68,730	8.379	£ 14,954	0.733	£20,400

Figure 60. Scatterplot of PSA results (1,000 simulations) – GT1b TE C

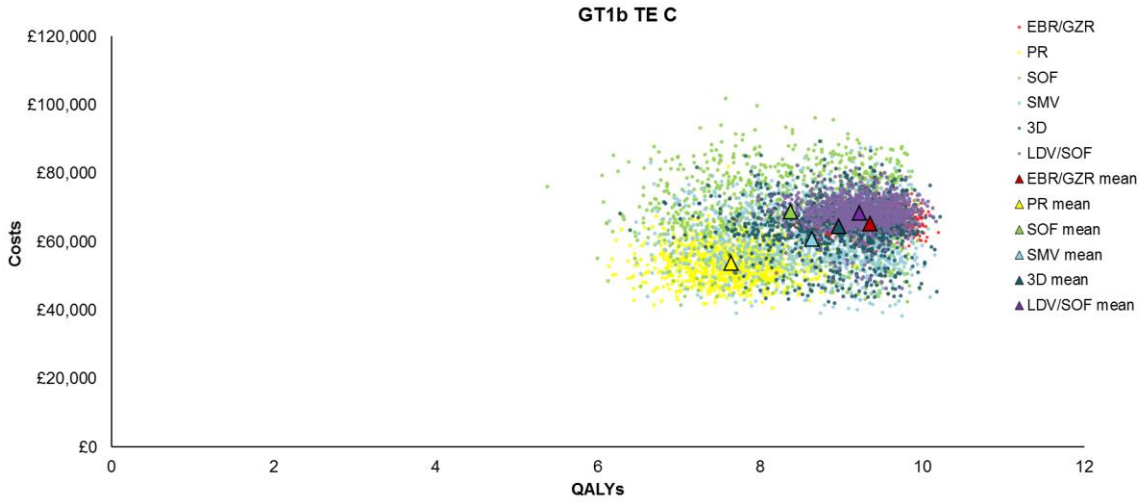
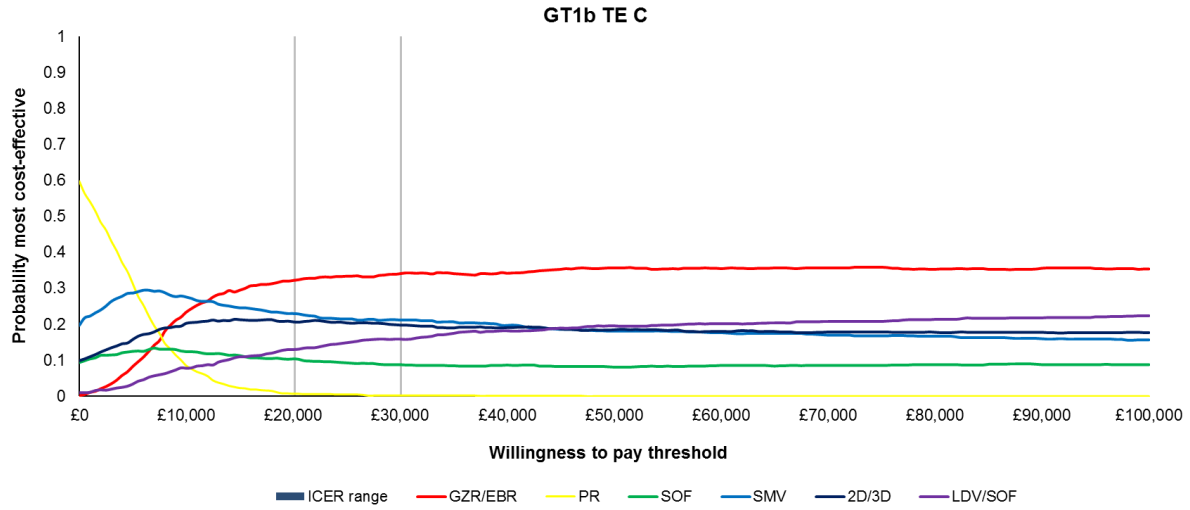


Figure 61. Cost-effectiveness acceptability curve – GT1b TE C



- **GT1b TE NC**

Table 128. Probabilistic sensitivity analysis results – GT1b TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 28,242	12.730	-	-	-
BSC	£ 28,838	11.298	£ 597	-1.432	Dominated
SMV	£ 35,017	14.038	£ 6,775	1.308	£5,180
2D/3D	£ 39,682	14.732	£ 11,440	2.002	£5,714
EBR/GZR	£ 40,602	14.805	£ 12,361	2.075	£5,956
LDV/SOF	£ 43,425	14.749	£ 15,183	2.019	£7,521
SOF	£ 44,666	14.181	£ 16,425	1.451	£11,318
DCV+SOF	£ 64,820	14.584	£ 36,578	1.854	£19,726

Figure 62. Scatterplot of PSA results (1,000 simulations) – GT1b TE NC

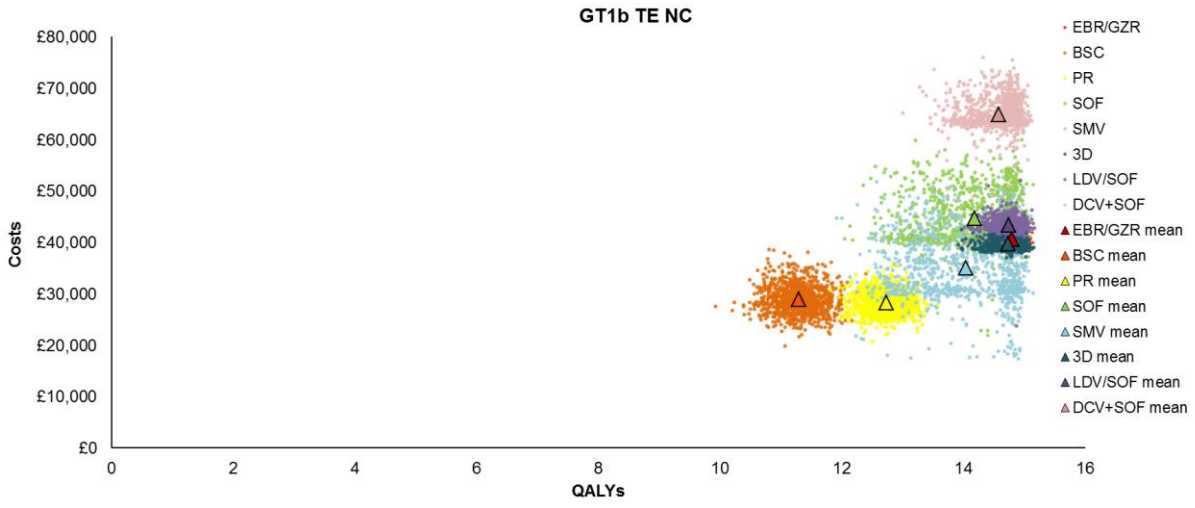
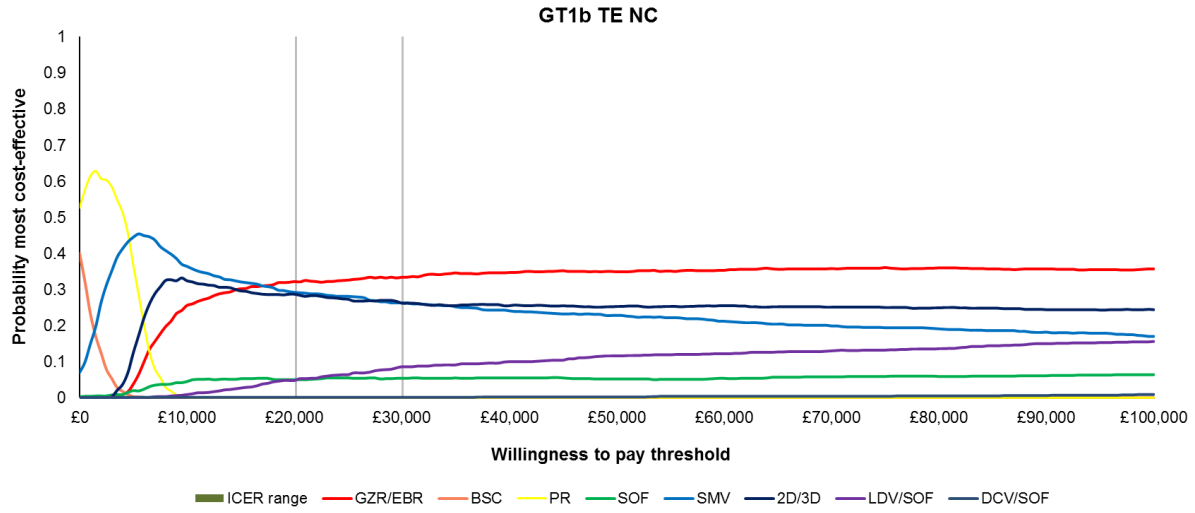


Figure 63. Cost-effectiveness acceptability curve – GT1b TE NC



- **GT4 TN C**

Table 129. Probabilistic sensitivity analysis results – GT4 TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 54,262	7.784	-	-	-
SMV	£ 63,721	8.529	£ 9,459	0.745	£12,697
SOF	£ 67,389	8.919	£ 13,127	1.135	£11,563
EBR/GZR	£ 68,610	9.290	£ 14,348	1.507	£9,524
LDV/SOF	£ 70,664	9.259	£ 16,403	1.475	£11,118
DCV/PR	£ 84,303	9.296	£ 30,041	1.512	£19,870
2D/3D	£ 92,284	9.229	£ 38,022	1.445	£26,316

Figure 64. Scatterplot of PSA results (1,000 simulations) – GT4 TN C

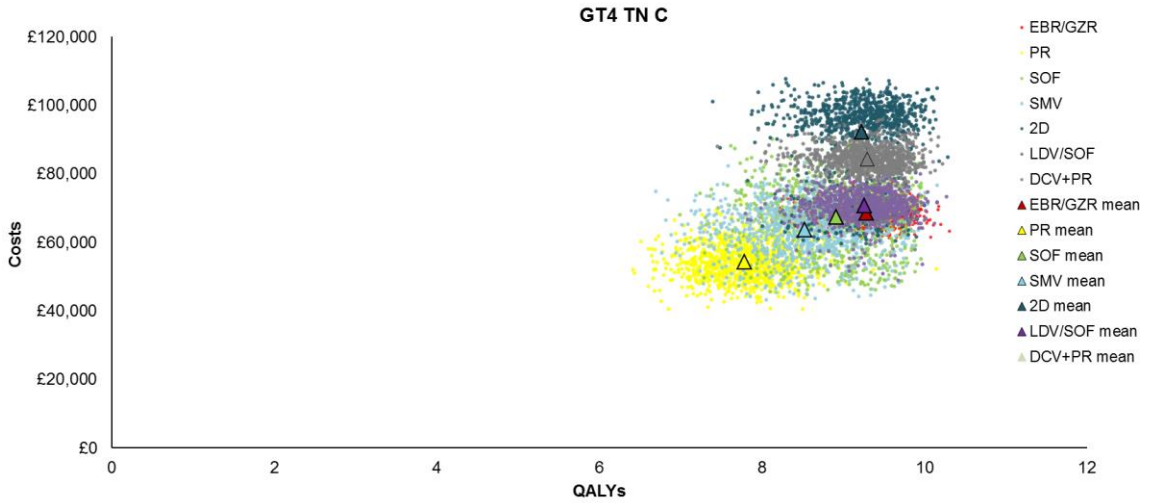
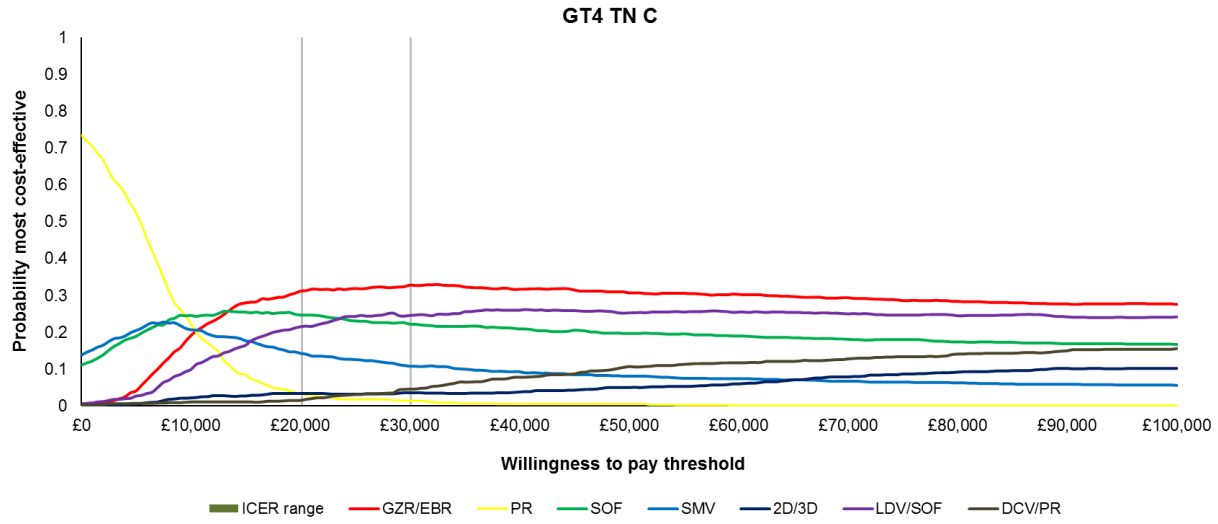


Figure 65. Cost-effectiveness acceptability curve – GT4 TN C



- **GT4 TN NC**

Table 130. Probabilistic sensitivity analysis results – GT4 TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 26,616	13.470	-	-	-
BSC	£ 30,411	11.403	£ 3,795	-2.067	Dominated
SMV	£ 35,604	14.573	£ 8,987	1.103	£8,151
2D/3D	£ 37,874	15.216	£ 11,258	1.745	£6,450
EBR/GZR	£ 42,356	15.152	£ 15,739	1.681	£9,362
DCV/PR	£ 58,261	15.162	£ 31,645	1.691	£18,713

Figure 66. Scatterplot of PSA results (1,000 simulations) – GT4 TN NC

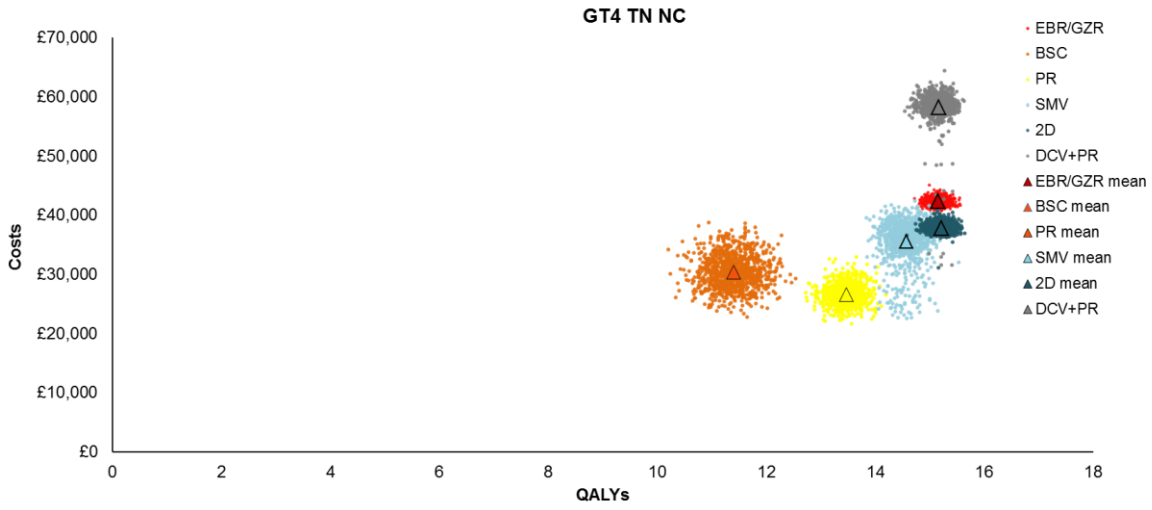
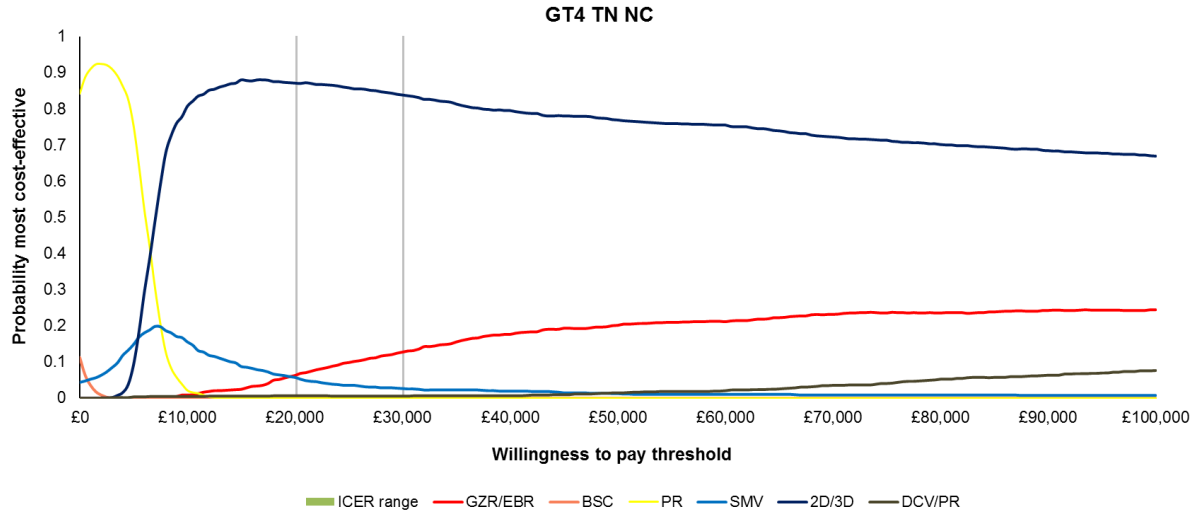


Figure 67. Cost-effectiveness acceptability curve – GT4 TN NC



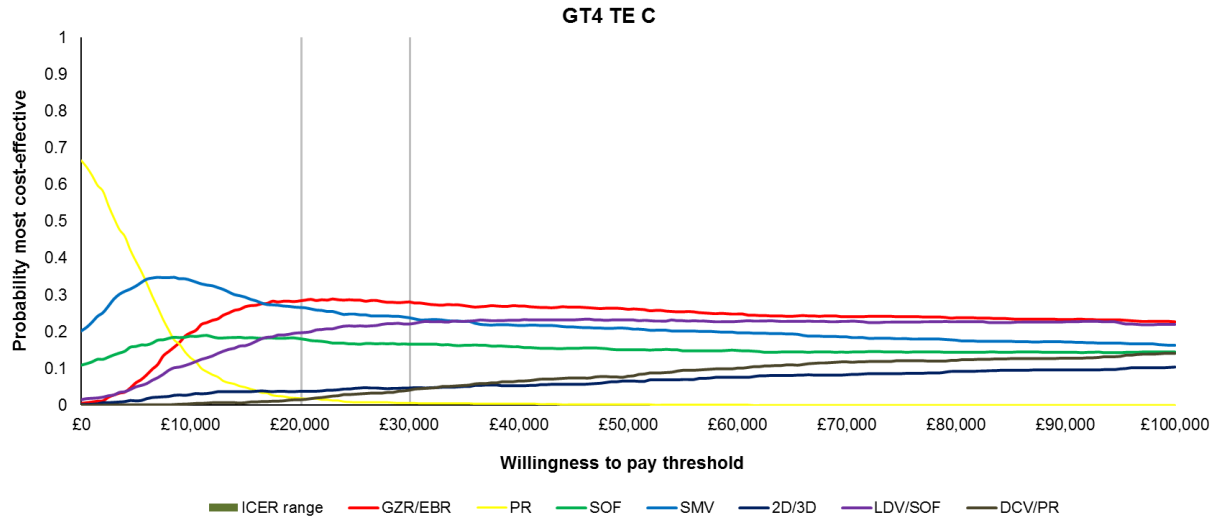
- **GT4 TE C**

Table 131. Probabilistic sensitivity analysis results – GT4 TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 54,299	7.561	-	-	-
SMV	£ 61,623	8.538	£ 7,324	0.977	£7,495
EBR/GZR	£ 67,144	9.129	£ 12,845	1.568	£8,192
SOF	£ 68,146	8.489	£ 13,847	0.928	£14,922
LDV/SOF	£ 69,386	9.079	£ 15,087	1.518	£9,940
DCV/PR	£ 83,232	9.121	£ 28,933	1.560	£18,545
2D/3D	£ 91,283	8.979	£ 36,984	1.418	£26,088

Figure 68. Scatterplot of PSA results (1,000 simulations) – GT4 TE C

Figure 69. Cost-effectiveness acceptability curve – GT4 TE C



- **GT4 TE NC**

Table 132. Probabilistic sensitivity analysis results – GT4 TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
PR	£ 27,687	12.835	-	-	-
BSC	£ 28,896	11.298	£ 1,208	-1.537	Dominated
SMV	£ 34,103	14.172	£ 6,416	1.336	£4,801
2D/3D	£ 37,779	14.643	£ 10,091	1.808	£5,582
EBR/GZR	£ 42,275	14.578	£ 14,588	1.742	£8,372
LDV/SOF	£ 44,050	14.652	£ 16,362	1.816	£9,008
DCV/PR	£ 58,259	14.560	£ 30,571	1.725	£17,722
DCV+SOF	£ 65,101	14.556	£ 37,414	1.720	£21,746

Figure 70. Scatterplot of PSA results (1,000 simulations) – GT4 TE NC

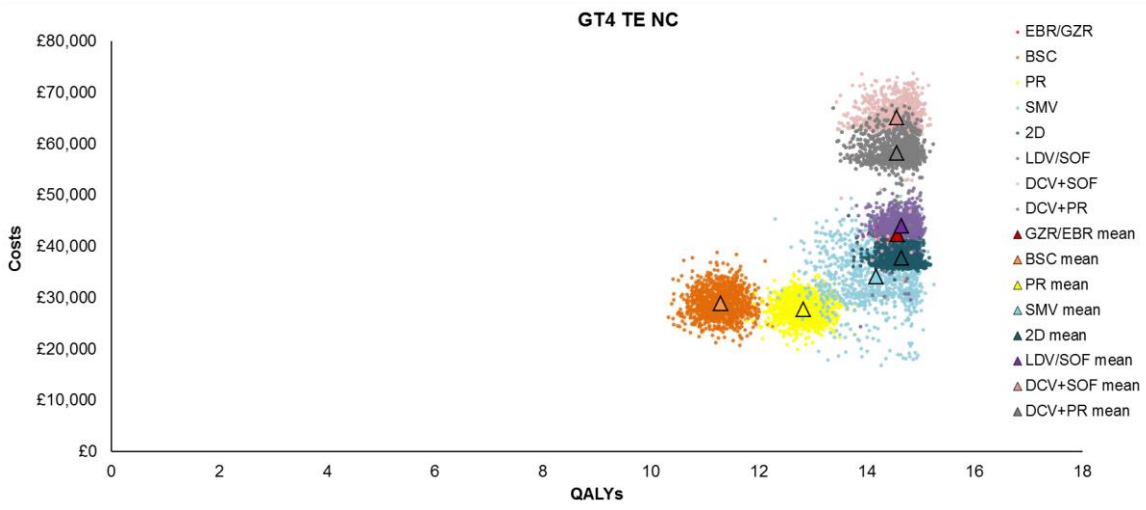
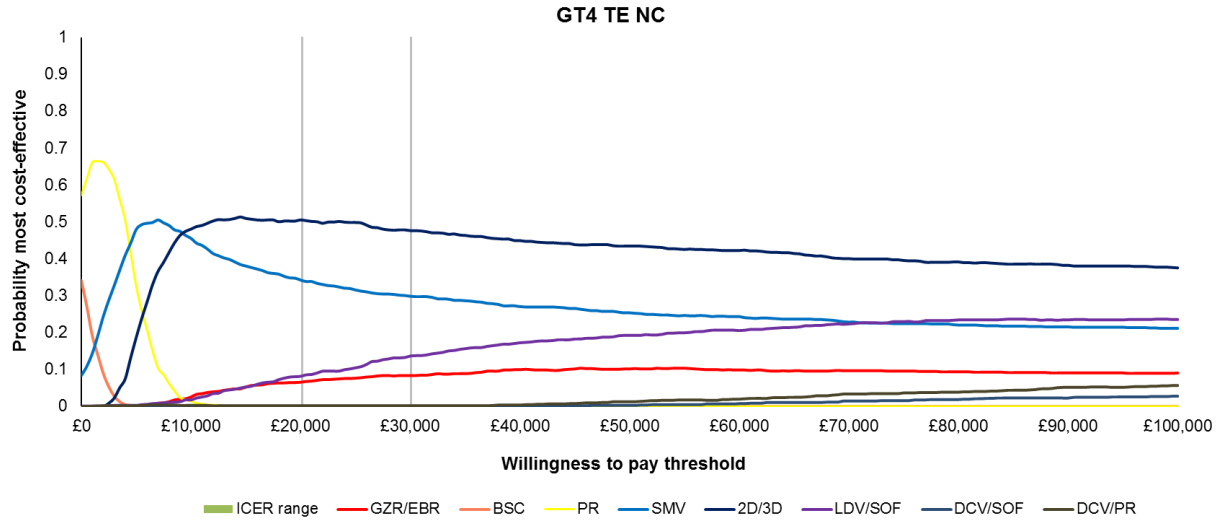


Figure 71. Cost-effectiveness acceptability curve – GT4 TE NC



5.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted for the following key variables using the 5% and 95% confidence intervals for the variables except when it is indicated otherwise:

- Cohort characteristics
  - Age (TN:30 and 50, TE:35 and 55)
  - Proportion of male (65% and 75%)
  - Baseline distribution to METAVIR fibrosis stages
  - Proportion of patients re-infected per year
  - Proportion of patients chronically infected following re-infection
- Transition probabilities
- Treatment characteristics
  - SVR rates
  - Discontinuation rate
  - AE rates
- Costs
  - Drug costs
  - Monitoring costs
  - Health state costs
  - AE costs
- Utilities
  - On-treatment utility decrements
  - Health state utilities
- Discount rates (0% and 6%)

The results of the deterministic sensitivity analyses for pairwise comparisons of EBR/GZR vs PR and of EBR/GZR are presented in figures below.

The inputs that most affect the economic results are the discount rates for utility and costs, the utility value for the F4 health state, the baseline age of the patients and the SVR rate for EBR/GZR in the GT1b population.

Figure 72. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables – GT1a TN C

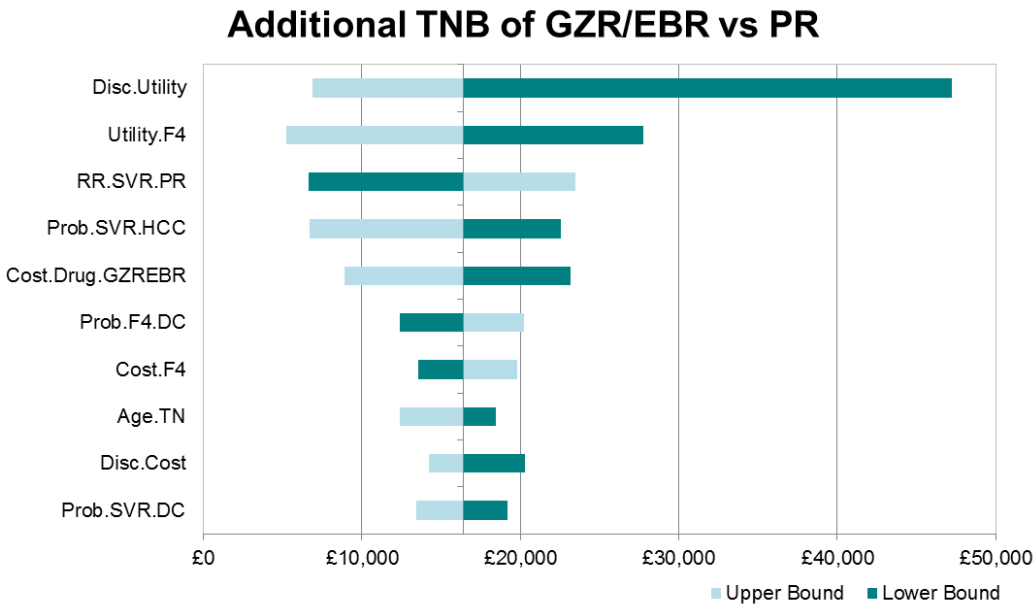


Figure 73. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables – GT1a TN NC

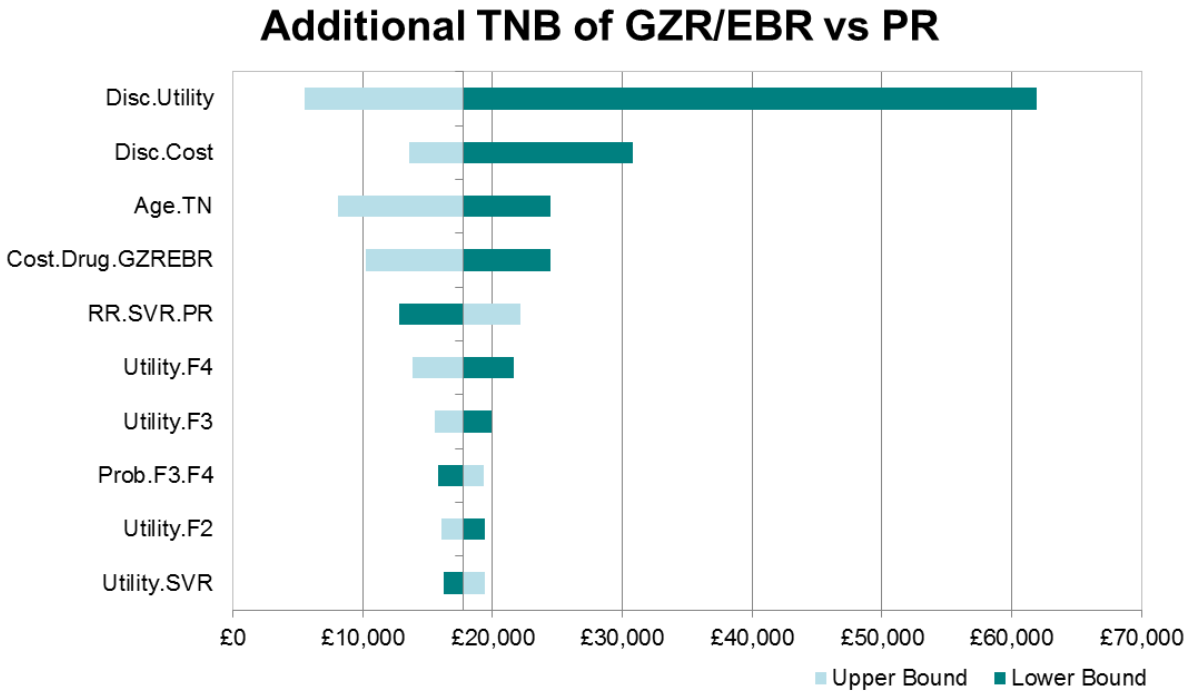


Figure 74. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables – GT1a TE C

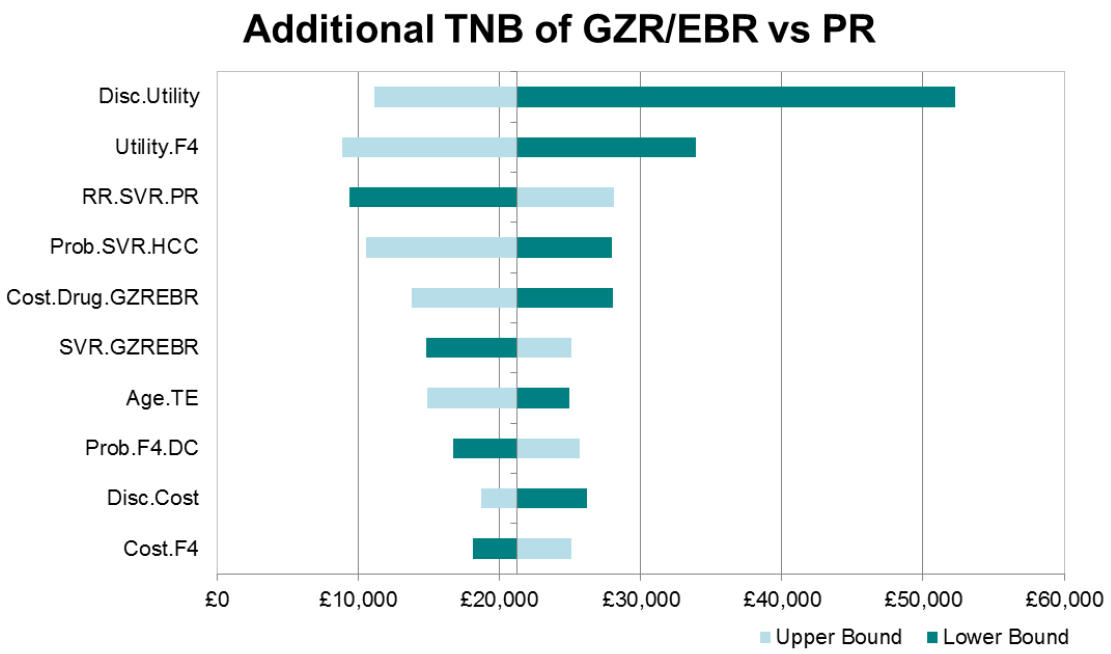


Figure 75. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables – GT1a TE NC

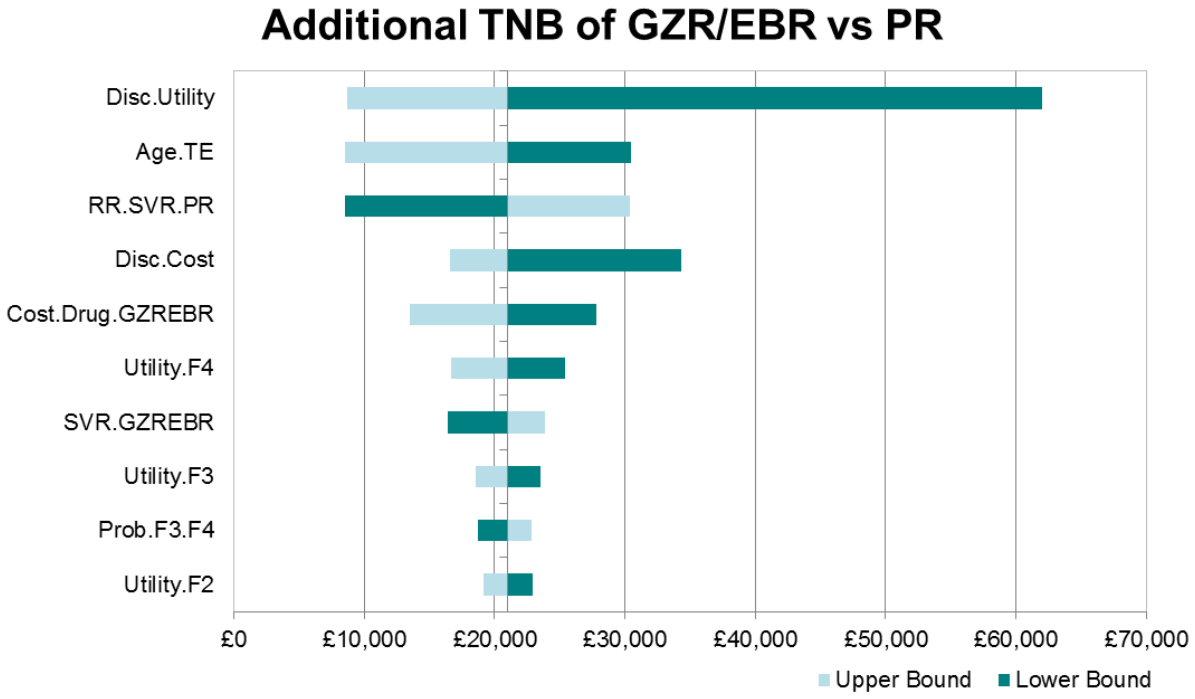


Figure 76. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables – GT1b TN C

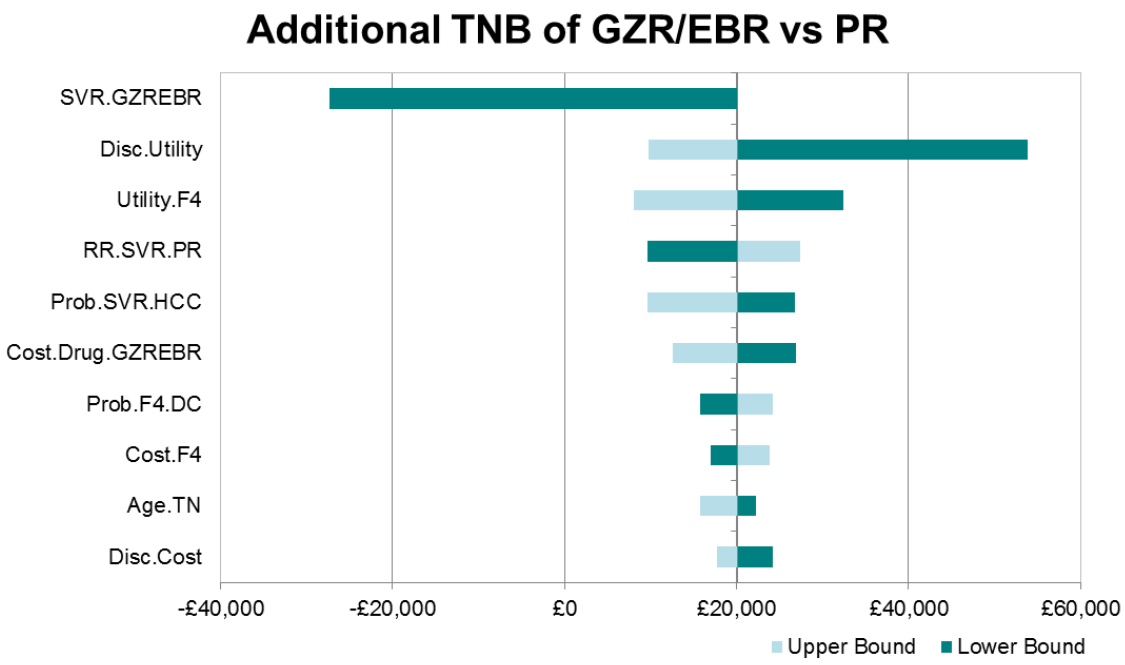


Figure 77. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables – GT1b TN NC

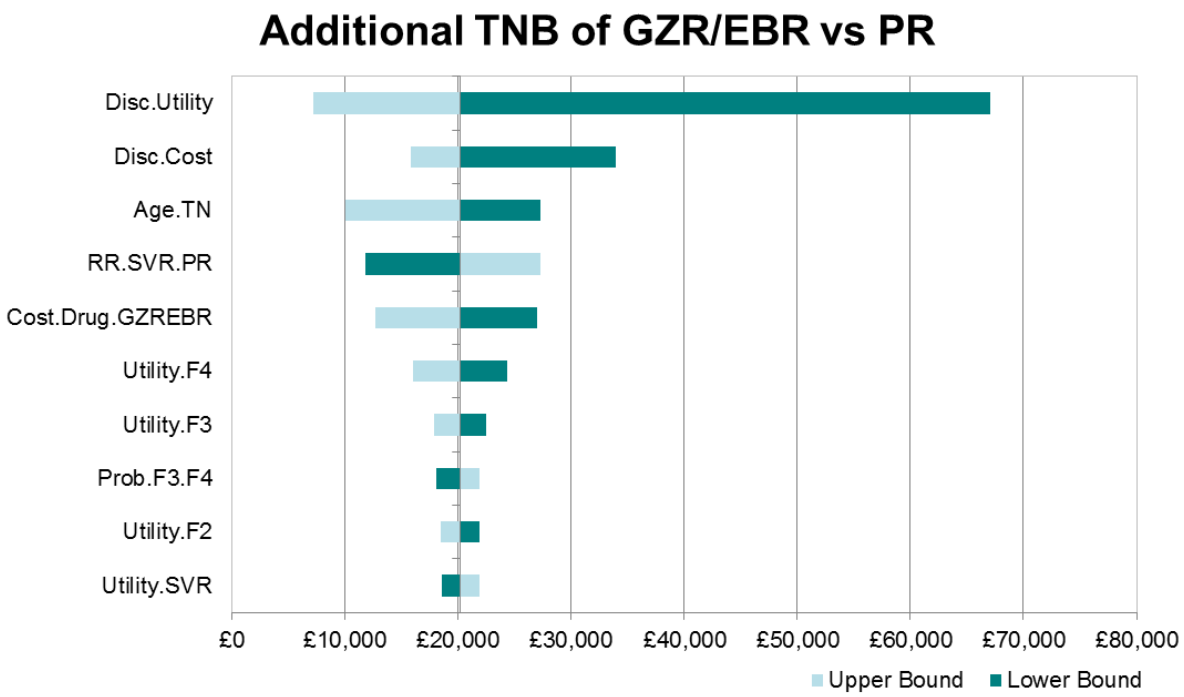


Figure 78. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables – GT1b TE C

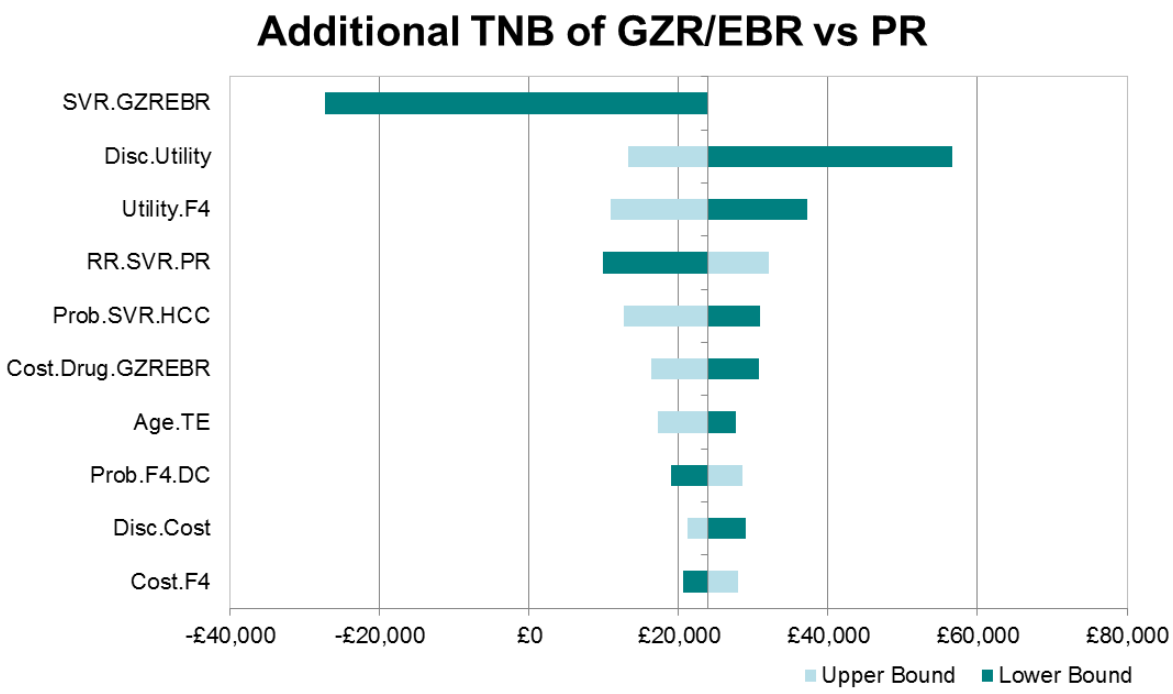


Figure 79. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables – GT1b TE NC

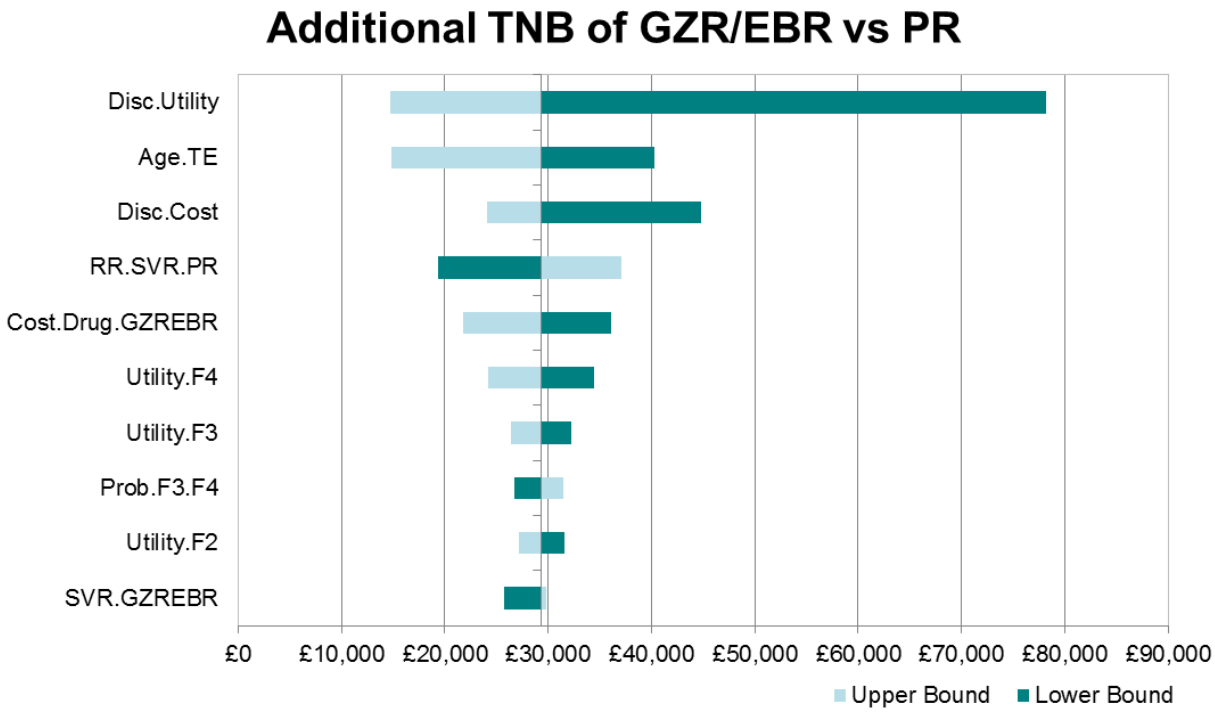


Figure 80. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables – GT4 TN NC

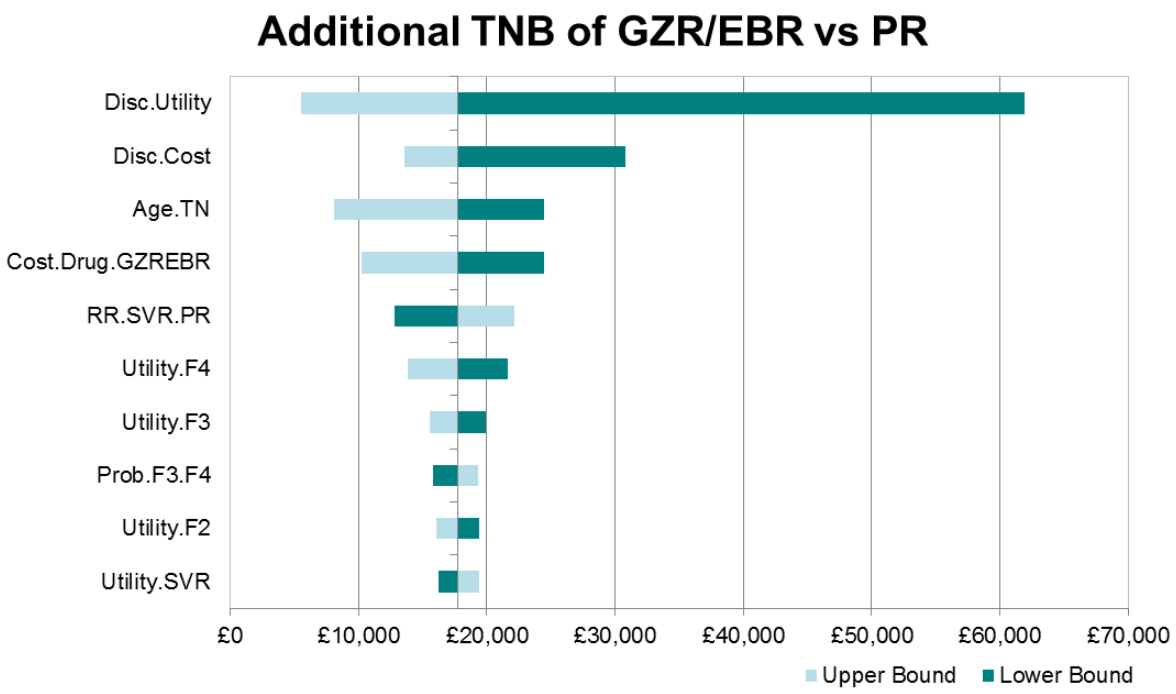
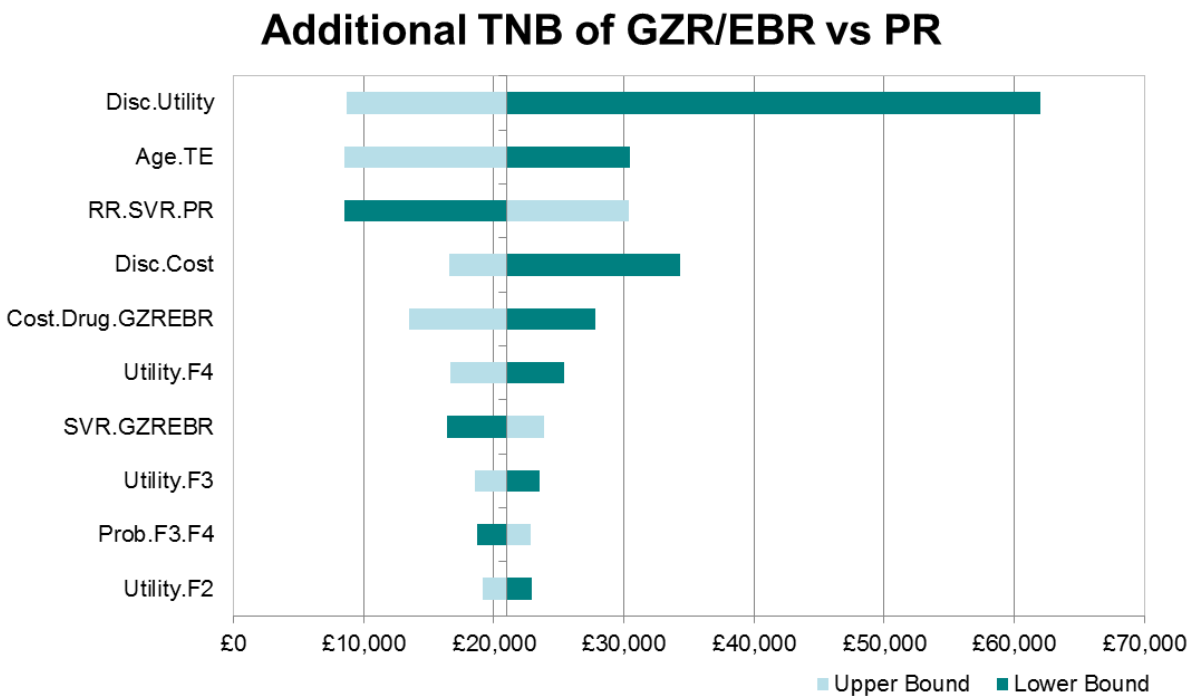


Figure 81. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables – GT4 TE NC



5.8.3 Scenario analyses

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural changes and alternative methodological assumptions.

- **Scenario analysis 1 – use of GT4 specific clinical data instead of applying GT1 data to GT4 in the base case**:

NMA results for SVR, AEs and discontinuation rates were used for GT4 subgroups for EBR/GZR and comparators when available. (Table 133, Table 134, Table 135). The results are presented in Table 136 to Table 139.

Table 133. SVR rates for EBR/GZR and relative risk of EBR/GZR versus comparators based on the NMA – scenario analysis 1

Regimen	Treatment duration (weeks)	Subgroups - SVR % (SE) for EBR/GZR and relative risk % (SE) of EBR/GZR versus comparators			
		GT4			
		TN		TE	
		C	NC	C	NC
EBR/GZR	12	100% (59.91%)	96.97% (2.77%)	66.67% (19.24%)	100% (36.17%)
BSC	0	Not applicable			
PR	48	5.26 (1.48)	2.36 (1.24)	2.47 (3.19)	2.59 (1.45)
SOF+PR	12/12	1.11 (1.45)		0.96 (3.93)	
SMV+PR	12/24	1.23 (3.59)	1.09 (2.47)	1.45 (5.42)	1.43 (2.68)
2D/3D	3D12RBV12				
	3D24RBV24				
	3D12				
	2D12RBV12		1.00 (1.57)		1.00 (1.49)
	2D24RBV24	1.02 (1.62)		0.68 (3.25)	
LDV/SOF	8				
	12	1.00 (1.29)		0.65 (2.77)	1.00 (1.32)
DCV	DCV12SOF12				1.00 (1.53)
	DCV24PR24	1.25 (2.44)	1.35 (2.91)	0.70 (3.62)	1.34 (2.57)

Abbreviations. 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; CIs: confidence intervals; DCV: daclatasvir-based regimen; EBR: elbasvir; GT: genotype; GZR: grazoprevir; LDV: ledipasvir; NC: non-cirrhotic; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained-virologic response; TE: treatment experienced; TN: treatment naïve

Table 134. Discontinuation rates for EBR/GZR and relative risks of EBR/GZR versus comparators based on the NMA – scenario analysis 1

Regimen	Treatment duration (weeks)	Subgroups - discontinuation % (SE) for EBR/GZR and relative risk % (SE) of EBR/GZR versus comparators			
		GT4			
		TN		TE	
		C	NC	C	NC
EBR/GZR	12	5.98% (9.12%)	0.52% (2.17%)	5.98% (9.12%)	0.52% (2.17%)
BSC	0	Not applicable			
PR	48	0.05 (9.11)	0.02 (5.36)	0.05 (9.11)	0.02 (5.36)
SOF+PR	12/12	0.09 (14.36)		0.09 (14.56)	
SMV+PR	12/24	1.77 (15.31)	0.81 (17.24)	1.77 (15.31)	0.81 (17.24)
2D/3D	3D12RBV12				
	3D24RBV24				
	3D12				
	2D12RBV12		0.67 (16.72)		0.67 (16.72)
	2D24RBV24	0.13 (15.68)		0.13 (15.68)	
LDV/SOF	8				
	12	2.99 (9.88)		2.99 (9.88)	0.64 (7.51)
DCV	DCV12SOF12				0.38 (15.95)
	DCV24PR24	0.08 (13.56)	0.03 (8.62)	0.08 (13.56)	0.03 (8.62)

Abbreviations. 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; CIs: confidence intervals; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 135. Adverse event rates (SE) for EBR/GZR and relative risks of EBR/GZR versus comparators based on the NMA – scenario analysis 1

Treatment	Aneamia	Nausea	Rash	Pruritus	Neutropenia
GT4 C					
EBR/GZR	0.0% (7.40%)	8.64% (9.80%)	0.0% (7.40%)	0.0% (7.4%)	0.0% (7.4%)
BSC	N/A	N/A	N/A	N/A	N/A
PR	0.03 (6.16)	0.25 (1.68)	0.09 (1.94)	0.03 (5.75)	0.03 (6.63)
SOF	0.06 (10.49)	0.17 (1.96)	0.18 (2.92)	0.08 (4.88)	0.13 (13.46)
SMV	0.08 (11.07)	0.21 (1.79)	0.08 (2.27)	0.05 (7.16)	0.23 (14.58)
3D/2D	0.03 (4.00)	0.28 (2.05)	0.21 (2.42)	0.06 (7.66)	0.01 (3.59)
LDV/SOF	1.85 (6.29)	0.85 (1.91)	0.47 (2.21)	0.25 (4.61)	0.00 (0.00)
DCV	0.04 (9.35)	0.00 (0.00)	0.00 (0.00)	0.03 (6.24)	0.06 (11.04)
GT4 NC					
EBR/GZR	0.0% (2.10%)	5.44% (3.16%)	0.0% (2.10%)	2.49% (2.63%)	0.0% (2.1%)
BSC	0	0	0	0	0
PR	0.01 (3.91)	0.40 (1.19)	0.10 (1.39)	0.01 (3.76)	0.01 (4.13)
SOF	N/A	N/A	N/A	N/A	N/A
SMV	0.04 (6.99)	0.41 (1.46)	0.12 (1.70)	0.03 (6.04)	0.13 (9.42)
3D/2D	0.75 (2.51)	1.28 (1.33)	0.75 (1.63)	0.08 (7.92)	0.64 (3.17)
LDV/SOF	0.61 (5.65)	1.11 (1.44)	0.26 (2.16)	0.37 (5.984)	0.00 (0.00)
DCV+SOF	0.58 (6.94)	0.50 (1.91)	0.73 (3.80)	0.54 (6.48)	0.03 (7.20)
DCV/PR	0.02 (5.94)	0.05 (1.91)	0.73 (3.80)	0.02 (5.50)	0.03 (7.20)

Abbreviations. AEs: adverse events; 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 136: Cost-effectiveness results – Scenario analysis 1 – GT4 TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£55,133	7.301	-	-	-
SOF	£58,091	9.062	£2,958	1.760	£1,681
SMV	£61,934	8.896	£6,801	1.595	£4,265
EBR/GZR	£66,679	9.355	£11,547	2.053	£5,623
DCV/PR	£68,818	8.819	£13,685	1.518	£9,017
LDV/SOF	£69,856	9.356	£14,724	2.054	£7,167
2D/3D	£81,714	9.335	£26,582	2.034	£13,069

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 137: Cost-effectiveness results – Scenario analysis 1 – GT4 TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£28,455	13.051	-	-	-
BSC	£30,513	11.404	£2,058	-1.647	Dominated
SMV	£34,610	14.867	£6,156	1.816	£3,390
2D/3D	£38,128	15.159	£9,673	2.109	£4,588
EBR/GZR	£42,264	15.159	£13,809	2.109	£6,549
DCV/PR	£60,947	14.192	£32,493	1.141	£28,471

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 138: Cost-effectiveness results – Scenario analysis 1 – GT4 TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£51,012	7.526	-	-	-
SOF	£60,316	8.533	£9,304	1.007	£9,241
DCV/PR	£63,018	9.193	£12,006	1.667	£7,204
SMV	£67,394	7.998	£16,382	0.472	£34,717
LDV/SOF	£67,447	9.337	£16,435	1.810	£9,078
EBR/GZR	£71,732	8.504	£20,720	0.978	£21,192
2D/3D	£79,311	9.318	£28,299	1.791	£15,797

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 139: Cost-effectiveness results – Scenario analysis 1 – GT4 TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£27,296	12.720	-	-	-
BSC	£28,835	11.271	£1,539	-1.449	Dominated
2D/3D	£36,171	14.834	£8,875	2.114	£4,198
SMV	£38,333	13.787	£11,037	1.067	£10,347
EBR/GZR	£40,306	14.834	£13,010	2.114	£6,154
LDV/SOF	£42,723	14.834	£15,427	2.114	£7,298
DCV/PR	£58,764	13.937	£31,468	1.217	£25,857
DCV+SOF	£62,995	14.826	£35,699	2.106	£16,952

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

- **Scenario analysis 2 – naïve comparison results:**

Implemented naïve comparison results instead of NMA results in the base case - for EBR/GZR and comparators with genotypes specific data (i.e. GT4 data used in GT4 subgroups). (Table 140, Table 141, Table 142). The results are presented from Table 143 to Table 154.

Table 140. SVR rates for EBR/GZR and relative risk of EBR/GZR versus comparators based on the naïve comparison – scenario analysis 2

Regimen	Treatment duration (weeks)	Subgroups SVR % for EBR/GZR versus comparators											
		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	96.2%	96.7%	91.1%	92.7%	100.0%	98.3%	100.0%	99.1%	96.2%	96.7%	91.1%	92.7%
BSC	0	SVR rates assumed to be 0%											
PR	48	2.77	1.9	3.46	2.42	2.86	1.95	3.53	2.54	2.77	1.9	3.46	2.42
SOF+PR	12/12	1.19	1.01	1.28	1.15	1.09	1.00	1.92	1.16	1.09		1.28	
SMV+PR	12/24	1.58	1.16	1.23	1.15	1.65	1.19	1.34	1.21	1.58	1.16	1.23	1.15
2D/3D	3D12RBV12		0.99		0.95	1.00		1.02					
	3D24RBV24	1.03		0.96									
	3D12						0.98		0.97				
	2D12RBV12										0.98		0.95
	2D24RBV24									1.00		0.96	
LDV/SOF	8		1.02				0.99						
	12	0.99		0.99	0.96	1.03		1.08	1.01	0.99		0.99	0.96
DCV	DCV12SOF12		0.98		0.92		0.97		0.97				0.92
	DCV24PR24									0.97	0.97	0.92	0.92

Abbreviations. 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; CIs: confidence intervals; DCV: daclatasvir-based regimen; EBR: elbasvir; GT: genotype; GZR: grazoprevir; LDV: ledipasvir; NC: non-cirrhotic; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained-virologic response; TE: treatment experienced; TN: treatment naïve

Table 141. Discontinuation rates for EBR/GZR and relative risks of EBR/GZR versus comparators based on the naïve comparison – scenario analysis 2

Regimen	Treatment duration (weeks)	Subgroups Discontinuation % for EBR/GZR versus comparators											
		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%
BSC	0	Not applicable											
PR	48	0.17	0.09	0.17	0.09	0.17	0.09	0.17	0.09	0.17	0.09	0.17	0.09
SOF+PR	12/12	0.06	0.26	0.06	0.26	0.06	0.26	0.06	0.26	0.06		0.06	
SMV+PR	12/24	0.22	0.09	0.22	0.09	0.22	0.09	0.22	0.09	0.22	0.09	0.22	0.09
2D/3D	3D12RBV12		0.56		0.56	0.22		0.22					
	3D24RBV24	0.18		0.18									
	3D12						5.8		5.8				
	2D12RBV12										5.8		5.8
	2D24RBV24									0.22		0.22	
LDV/SOF	8		6.06		6.06		6.06		6.06				0.72
	12	1.56		1.56		1.56		1.56		1.56		1.56	
DCV	DCV12SOF12		5.18		5.18		5.18		5.18				5.18
	DCV24PR24									5.18	5.18	5.18	5.18

Abbreviations. 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; CIs: confidence intervals; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 142. Adverse event rates for EBR/GZR versus comparators based on the naïve comparison – scenario analysis 2

Treatment	Aneamia	Nausea	Rash	Pruritus	Neutropenia
GT1 C					
EBR/GZR	0.4%	3.0%	3.0%	1.5%	0.4%
BSC	N/A	N/A	N/A	N/A	N/A
PR	0.02	0.29	0.15	0.1	0.02
SOF	0.02	0.24	0.34	0.19	0.04
SMV	0.02	0.25	0.14	0.09	0.02
3D/2D	0.04	0.29	0.26	0.37	0.02
LDV/SOF	0.74	0.77	0.77	0.59	0.00
DCV	N/A	N/A	N/A	N/A	N/A
GT1 NC					
EBR/GZR	0.1%	10.3%	2.2%	2.1%	0.2%
BSC	0	0	0	0	0
PR	0.02	0.40	0.10	0.05	0.01
SOF	0.03	0.59	0.25	0.24	0.01
SMV	0.02	0.41	0.11	0.06	0.01
3D/2D	0.06	0.54	0.29	0.17	0.57
LDV/SOF	0.4	1.46	1.69	2.78	0.00
DCV	4.14	0.54	0.48	0.97	0.05
GT4 C					
EBR/GZR	0.4%	3.0%	3.0%	1.5%	0.4%
BSC	N/A	N/A	N/A	N/A	N/A
PR	0.02	0.29	0.15	0.1	0.02
SOF	0.02	0.24	0.34	0.19	0.04
SMV	0.02	0.25	0.14	0.09	0.02
3D/2D	0.06	0.33	0.35	0.53	0.02
LDV/SOF	0.74	0.77	0.77	0.59	0.00
DCV	4.14	0.54	0.48	0.97	0.05
GT4 NC					
EBR/GZR	0.1%	10.3%	2.2%	2.1%	0.2%
BSC	0	0	0	0	0
PR	0.02	0.40	0.10	0.05	0.01
SOF	N/A	N/A	N/A	N/A	N/A
SMV	0.02	0.41	0.11	0.06	0.01
3D/2D	1.00	1.25	0.7	0.39	3.19
LDV/SOF	N/A	N/A	N/A	N/A	N/A
DCV	4.14	0.54	0.48	0.97	0.05

Abbreviations. AEs: adverse events; 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 143. Cost-effectiveness results – Scenario analysis 2 – GT1a TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,917	7.728	-	-	-
SMV	£67,151	8.378	£12,234	0.650	£18,822
EBR/GZR	£68,555	9.260	£13,639	1.531	£8,906
LDV/SOF	£70,843	9.285	£15,926	1.556	£10,233
SOF	£71,293	8.832	£16,376	1.104	£14,838
2D/3D	£102,717	9.242	£47,800	1.513	£31,584

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 144. Cost-effectiveness results – Scenario analysis 2 – GT1a TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,929	13.433	-	-	-
BSC	£30,513	11.404	£3,584	-2.030	Dominated
LDV/SOF	£32,325	15.062	£5,396	1.629	£3,313
SMV	£36,160	14.655	£9,231	1.222	£7,554
2D/3D	£40,818	15.187	£13,889	1.753	£7,921
EBR/GZR	£42,389	15.150	£15,460	1.716	£9,008
SOF	£43,012	15.080	£16,084	1.647	£9,768
DCV+SOF	£64,942	15.217	£38,013	1.783	£21,317

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 145. Cost-effectiveness results – Scenario analysis 2 – GT1a TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,419	7.553	-	-	-
SMV	£61,847	8.695	£7,428	1.141	£6,507
EBR/GZR	£67,287	9.116	£12,868	1.563	£8,233
LDV/SOF	£69,586	9.139	£15,167	1.586	£9,563
SOF	£71,058	8.585	£16,639	1.031	£16,132
2D/3D	£99,987	9.265	£45,568	1.711	£26,628

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 146. Cost-effectiveness results – Scenario analysis 2 – GT1a TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£28,495	12.727	-	-	-
BSC	£28,835	11.271	£340	-1.456	Dominated
SMV	£35,580	14.154	£7,085	1.428	£4,962
2D/3D	£39,712	14.748	£11,217	2.022	£5,549
EBR/GZR	£42,298	14.578	£13,804	1.851	£7,455
LDV/SOF	£43,733	14.713	£15,239	1.986	£7,673
SOF	£45,840	14.123	£17,346	1.397	£12,421
DCV+SOF	£63,459	14.827	£34,964	2.100	£16,650

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 147. Cost-effectiveness results – Scenario analysis 2 – GT1b TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,868	7.734	-	-	-
2D/3D	£66,491	9.356	£11,623	1.622	£7,166
SMV	£67,217	8.371	£12,349	0.637	£19,394
EBR/GZR	£67,714	9.356	£12,846	1.622	£7,918
SOF	£68,864	9.111	£13,996	1.377	£10,166
LDV/SOF	£70,869	9.282	£16,001	1.548	£10,338

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 148. Cost-effectiveness results – Scenario analysis 2 – GT1b TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£27,066	13.414	-	-	-
BSC	£30,513	11.404	£3,447	-2.011	Dominated
LDV/SOF	£31,101	15.231	£4,035	1.817	£2,221
SMV	£36,378	14.625	£9,312	1.211	£7,691
2D/3D	£40,037	15.274	£12,970	1.860	£6,974
EBR/GZR	£41,963	15.209	£14,896	1.794	£8,303
SOF	£42,322	15.175	£15,256	1.761	£8,665
DCV+SOF	£64,582	15.266	£37,516	1.852	£20,259

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 149. Cost-effectiveness results – Scenario analysis 2 – GT1b TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£53,984	7.602	-	-	-
SMV	£61,729	8.708	£7,745	1.106	£7,001
2D/3D	£64,520	9.288	£10,536	1.686	£6,248
EBR/GZR	£65,304	9.337	£11,320	1.736	£6,522
LDV/SOF	£69,467	9.152	£15,483	1.551	£9,984
SOF	£75,339	8.108	£21,355	0.506	£42,208

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 150. Cost-effectiveness results – Scenario analysis 2 – GT1b TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£28,305	12.752	-	-	-
BSC	£28,835	11.271	£530	-1.481	Dominated
SMV	£35,226	14.201	£6,922	1.449	£4,776
2D/3D	£38,913	14.835	£10,608	2.083	£5,093
EBR/GZR	£40,595	14.804	£12,290	2.052	£5,989
LDV/SOF	£43,305	14.770	£15,000	2.018	£7,434
SOF	£44,554	14.294	£16,250	1.542	£10,540
DCV+SOF	£63,459	14.827	£35,154	2.075	£16,944

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 151. Cost-effectiveness results – Scenario analysis 2 – GT4 TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,917	7.728	-	-	-
SMV	£67,151	8.378	£12,234	0.650	£18,822
EBR/GZR	£68,555	9.260	£13,639	1.531	£8,906
SOF	£69,636	9.022	£14,719	1.294	£11,377
LDV/SOF	£70,843	9.285	£15,926	1.556	£10,233
DCV/PR	£84,136	9.327	£29,219	1.599	£18,279
2D/3D	£96,662	9.313	£41,745	1.585	£26,340

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 152. Cost-effectiveness results – Scenario analysis 2 – GT4 TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,929	13.433	-	-	-
BSC	£30,513	11.404	£3,584	-2.030	Dominated
SMV	£36,160	14.655	£9,231	1.222	£7,554
2D/3D	£37,792	15.225	£10,863	1.791	£6,064
EBR/GZR	£42,389	15.150	£15,460	1.716	£9,008
DCV/PR	£57,934	15.246	£31,005	1.812	£17,108

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 153. Cost-effectiveness results – Scenario analysis 2 – GT4 TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,419	7.553	-	-	-
SMV	£61,847	8.695	£7,428	1.141	£6,507
EBR/GZR	£67,287	9.116	£12,868	1.563	£8,233
LDV/SOF	£69,586	9.139	£15,167	1.586	£9,563
SOF	£71,058	8.585	£16,639	1.031	£16,132
DCV/PR	£81,771	9.305	£27,352	1.752	£15,614
2D/3D	£94,554	9.265	£40,135	1.712	£23,450

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 154. Cost-effectiveness results – Scenario analysis 2 – GT4 TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£28,495	12.727	-	-	-
BSC	£28,835	11.271	£340	-1.456	Dominated
SMV	£35,580	14.154	£7,085	1.428	£4,962
2D/3D	£36,960	14.748	£8,465	2.022	£4,187
EBR/GZR	£42,298	14.578	£13,804	1.851	£7,455
LDV/SOF	£43,733	14.713	£15,239	1.986	£7,673
DCV/PR	£56,735	14.820	£28,240	2.093	£13,493
DCV+SOF	£63,459	14.827	£34,964	2.100	£16,650

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

- **Scenario analysis 3 – transition probabilities across fibrosis health states:**

Grishchenko et al, 2009 transition probabilities were used instead of probabilities from Thein et al, 2008 in the base case. [112, 139]These report different fibrosis progression rates by age at presentation for treatment ([30-39] versus [40-49] versus [50-59] years old). Results are presented from Table 156 to Table 167.

Table 155. Transition probabilities used in scenario analysis 3

	Mean value per age range			Source
	[30-39]	[40-49]	[50-59]	
Non-GT1				
F0 to F1	0.015	0.023	0.035	Grishchenko et al, 2009 [112]
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	
GT1				
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	

Abbreviations. DC: decompensated cirrhosis; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis; HCC: hepatocellular carcinoma; LD: liver disease; LT: liver transplant (1st year); PLT: post liver transplant (subsequent years); SVR: sustained-virologic response

Table 156. Cost-effectiveness results – Scenario analysis 3 – GT1a TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,599	7.741	-	-	-
SOF	£64,907	8.845	£10,308	1.104	£9,338
SMV	£65,380	8.456	£10,781	0.714	£15,095
EBR/GZR	£68,555	9.260	£13,956	1.518	£9,193
LDV/SOF	£70,941	9.259	£16,342	1.518	£10,765
2D/3D	£96,765	9.208	£42,166	1.467	£28,742

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 157. Cost-effectiveness results – Scenario analysis 3 – GT1a TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£18,101	13.474	£1,896	1.072	£1,768 (PR vs)
PR	£19,996	14.546	-	-	-
LDV/SOF	£30,010	15.389	£10,014	0.843	£11,881
SMV	£33,052	15.115	£13,055	0.569	£22,945
2D/3D	£38,750	15.460	£18,754	0.914	£20,509
EBR/GZR	£40,448	15.422	£20,452	0.876	£23,347
SOF	£41,420	15.299	£21,424	0.753	£28,466
DCV+SOF	£63,173	15.453	£43,176	0.907	£47,628

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 158. Cost-effectiveness results – Scenario analysis 3 – GT1a TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£55,175	7.447	-	-	-
SMV	£61,679	8.592	£6,504	1.145	£5,681
SOF	£65,426	8.513	£10,252	1.066	£9,616
EBR/GZR	£67,287	9.116	£12,113	1.669	£7,257
LDV/SOF	£69,467	9.139	£14,292	1.692	£8,448
2D/3D	£94,679	9.160	£39,504	1.713	£23,062

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 159. Cost-effectiveness results – Scenario analysis 3 – GT1a TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£17,324	13.128	£3,395	0.812	£4,180 (PR vs)
PR	£20,719	13.940	-	-	-
SMV	£31,933	14.665	£11,214	0.725	£15,477
2D/3D	£38,321	14.934	£17,602	0.994	£17,716
EBR/GZR	£40,311	14.864	£19,592	0.924	£21,207
SOF	£42,113	14.651	£21,394	0.711	£30,095
LDV/SOF	£42,154	14.934	£21,435	0.994	£21,571
DCV+SOF	£62,904	14.908	£42,185	0.968	£43,594

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 160. Cost-effectiveness results – Scenario analysis 3 – GT1b TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,884	7.709	-	-	-
SOF	£62,628	9.107	£7,743	1.398	£5,538
2D/3D	£64,947	9.327	£10,062	1.618	£6,217
SMV	£65,571	8.434	£10,687	0.725	£14,741
EBR/GZR	£67,714	9.356	£12,829	1.647	£7,787
LDV/SOF	£70,320	9.331	£15,436	1.622	£9,517

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 161. Cost-effectiveness results – Scenario analysis 3 – GT1b TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£18,101	13.474	£2,030	1.056	£1,922 (PR vs)
PR	£20,131	14.530	-	-	-
LDV/SOF	£29,912	15.400	£9,782	0.870	£11,246
SMV	£33,277	15.089	£13,146	0.558	£23,541
2D/3D	£38,564	15.472	£18,433	0.941	£19,582
EBR/GZR	£40,188	15.452	£20,058	0.922	£21,757
SOF	£40,387	15.419	£20,256	0.889	£22,797
DCV+SOF	£63,244	15.444	£43,113	0.914	£47,176

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 162. Cost-effectiveness results – Scenario analysis 3 – GT1b TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,008	7.577	-	-	-
SMV	£59,760	8.806	£5,751	1.229	£4,680
2D/3D	£62,754	9.285	£8,746	1.708	£5,122
EBR/GZR	£65,304	9.337	£11,296	1.760	£6,418
SOF	£66,777	8.363	£12,769	0.786	£16,253
LDV/SOF	£67,689	9.337	£13,681	1.760	£7,773

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 163. Cost-effectiveness results – Scenario analysis 3 – GT1b TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£17,324	13.128	£3,745	0.773	£4,845 (PR vs)
PR	£21,069	13.901	-	-	-
SMV	£32,052	14.651	£10,984	0.750	£14,637
2D/3D	£37,667	14.997	£16,598	1.096	£15,143
EBR/GZR	£39,267	14.981	£18,198	1.080	£16,848
SOF	£41,673	14.700	£20,604	0.799	£25,775
LDV/SOF	£41,732	14.981	£20,663	1.080	£19,131
DCV+SOF	£62,322	14.973	£41,253	1.072	£38,479

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 164. Cost-effectiveness results – Scenario analysis 3 – GT4 TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,599	7.741	-	-	-
SOF	£63,401	9.018	£8,802	1.277	£6,894
SMV	£65,380	8.456	£10,781	0.714	£15,095
EBR/GZR	£68,555	9.260	£13,956	1.518	£9,193
LDV/SOF	£70,941	9.259	£16,342	1.518	£10,765
DCV/PR	£84,350	9.301	£29,750	1.560	£19,076
2D/3D	£93,333	9.282	£38,734	1.541	£25,138

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 165. Cost-effectiveness results – Scenario analysis 3 – GT4 TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£20,250	13.124	£818	1.249	£655 (PR vs)
PR	£21,069	14.373	-	-	-
SMV	£33,575	15.033	£12,507	0.660	£18,959
2D/3D	£36,223	15.437	£15,154	1.064	£14,244
EBR/GZR	£40,655	15.392	£19,586	1.019	£19,224
DCV/PR	£56,630	15.418	£35,561	1.045	£34,033

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 166. Cost-effectiveness results – Scenario analysis 3 – GT4 TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,551	7.517	-	-	-
SMV	£61,311	8.633	£6,760	1.116	£6,055
SOF	£65,426	8.513	£10,875	0.997	£10,911
EBR/GZR	£67,287	9.116	£12,736	1.600	£7,962
LDV/SOF	£69,467	9.139	£14,916	1.622	£9,194
DCV/PR	£82,894	9.178	£28,343	1.662	£17,054
2D/3D	£91,857	9.164	£37,306	1.647	£22,645

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 167. Cost-effectiveness results – Scenario analysis 3 – GT4 TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£19,299	12.815	£2,599	0.939	£2,768 (PR vs)
PR	£21,898	13.754	-	-	-
SMV	£32,370	14.597	£10,472	0.843	£12,419
2D/3D	£35,798	14.909	£13,900	1.155	£12,036
EBR/GZR	£40,554	14.828	£18,656	1.074	£17,378
LDV/SOF	£42,325	14.909	£20,427	1.155	£17,689
DCV/PR	£56,380	14.873	£34,482	1.118	£30,832
DCV+SOF	£63,094	14.880	£41,196	1.126	£36,593

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

- **Scenario analysis 4 – SVR related utility increment:**

SVR related utility increments based on European patients from the EBR/GZR clinical trials (0.03) was used instead of SVR related utility increments from the Wright et al 2006 study (0.05). [23] Results are presented from Table 168 to Table 179.

Table 168. Cost-effectiveness results – Scenario analysis 4 – GT1a TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,599	7.643	-	-	-
SOF	£64,907	8.617	£10,308	0.974	£10,584
SMV	£65,380	8.278	£10,781	0.634	£16,992
EBR/GZR	£68,555	8.991	£13,956	1.348	£10,357
LDV/SOF	£70,941	8.991	£16,342	1.347	£12,128
2D/3D	£96,765	8.952	£42,166	1.308	£32,228

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 169. Cost-effectiveness results – Scenario analysis 4 – GT1a TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,580	13.293	-	-	-
BSC	£30,513	11.404	£3,932	-1.890	Dominated
LDV/SOF	£32,059	14.759	£5,479	1.465	£3,739
SMV	£36,693	14.267	£10,113	0.974	£10,382
2D/3D	£40,479	14.875	£13,899	1.582	£8,784
EBR/GZR	£42,389	14.808	£15,809	1.515	£10,438
SOF	£43,855	14.616	£17,275	1.323	£13,062
DCV+SOF	£64,902	14.868	£38,321	1.574	£24,340

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 170. Cost-effectiveness results – Scenario analysis 4 – GT1a TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£55,175	7.387	-	-	-
SMV	£61,679	8.403	£6,504	1.016	£6,400
SOF	£65,426	8.327	£10,252	0.940	£10,903
EBR/GZR	£67,287	8.869	£12,113	1.482	£8,172
LDV/SOF	£69,467	8.890	£14,292	1.503	£9,512
2D/3D	£94,679	8.915	£39,504	1.528	£25,858

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 171. Cost-effectiveness results – Scenario analysis 4 – GT1a TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£27,836	12.671	-	-	-
BSC	£28,835	11.271	£999	-1.400	Dominated
SMV	£34,982	13.928	£7,146	1.257	£5,685
2D/3D	£39,915	14.387	£12,079	1.715	£7,042
EBR/GZR	£42,298	14.265	£14,462	1.594	£9,075
LDV/SOF	£43,747	14.387	£15,911	1.715	£9,276
SOF	£45,111	13.919	£17,275	1.247	£13,848
DCV+SOF	£64,599	14.347	£36,763	1.676	£21,936

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 172. Cost-effectiveness results – Scenario analysis 4 – GT1b TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,884	7.614	-	-	-
SOF	£62,628	8.850	£7,743	1.236	£6,264
2D/3D	£64,947	9.050	£10,062	1.436	£7,005
SMV	£65,571	8.258	£10,687	0.644	£16,593
EBR/GZR	£67,714	9.077	£12,829	1.463	£8,771
LDV/SOF	£70,320	9.054	£15,436	1.440	£10,719

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 173. Cost-effectiveness results – Scenario analysis 4 – GT1b TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,800	13.266	-	-	-
BSC	£30,513	11.404	£3,712	-1.862	Dominated
LDV/SOF	£31,899	14.779	£5,099	1.513	£3,370
SMV	£37,062	14.221	£10,262	0.956	£10,740
2D/3D	£40,232	14.895	£13,432	1.630	£8,242
EBR/GZR	£41,963	14.861	£15,162	1.595	£9,504
SOF	£42,161	14.828	£15,361	1.562	£9,834
DCV+SOF	£65,018	14.853	£38,218	1.587	£24,076

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 174. Cost-effectiveness results – Scenario analysis 4 – GT1b TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,008	7.503	-	-	-
SMV	£59,760	8.594	£5,751	1.091	£5,271
2D/3D	£62,754	9.019	£8,746	1.516	£5,769
EBR/GZR	£65,304	9.066	£11,296	1.563	£7,225
SOF	£66,777	8.193	£12,769	0.690	£18,500
LDV/SOF	£67,689	9.066	£13,681	1.563	£8,751

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 175. Cost-effectiveness results – Scenario analysis 4 – GT1b TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£28,407	12.603	-	-	-
BSC	£28,835	11.271	£428	-1.332	Dominated
SMV	£35,177	13.905	£6,770	1.302	£5,199
2D/3D	£38,905	14.497	£10,499	1.894	£5,544
EBR/GZR	£40,595	14.469	£12,188	1.866	£6,532
LDV/SOF	£43,060	14.469	£14,654	1.866	£7,854
SOF	£44,393	14.005	£15,987	1.402	£11,406
DCV+SOF	£63,650	14.461	£35,244	1.858	£18,970

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 176. Cost-effectiveness results – Scenario analysis 4 – GT4 TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,599	7.643	-	-	-
SOF	£63,401	8.771	£8,802	1.128	£7,804
SMV	£65,380	8.278	£10,781	0.634	£16,992
EBR/GZR	£68,555	8.991	£13,956	1.348	£10,357
LDV/SOF	£70,941	8.991	£16,342	1.347	£12,128
DCV/PR	£84,350	9.029	£29,750	1.386	£21,471
2D/3D	£93,333	9.018	£38,734	1.375	£28,176

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 177. Cost-effectiveness results – Scenario analysis 4 – GT4 TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,580	13.293	-	-	-
BSC	£30,513	11.404	£3,932	-1.890	Dominated
SMV	£36,693	14.267	£10,113	0.974	£10,382
2D/3D	£37,785	14.876	£11,204	1.583	£7,080
EBR/GZR	£42,389	14.808	£15,809	1.515	£10,438
DCV/PR	£58,178	14.861	£31,598	1.568	£20,153

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 178. Cost-effectiveness results – Scenario analysis 4 – GT4 TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£54,551	7.449	-	-	-
SMV	£61,311	8.440	£6,760	0.991	£6,821
SOF	£65,426	8.327	£10,875	0.878	£12,381
EBR/GZR	£67,287	8.869	£12,736	1.420	£8,967
LDV/SOF	£69,467	8.890	£14,916	1.441	£10,353
DCV/PR	£82,894	8.926	£28,343	1.477	£19,189
2D/3D	£91,857	8.919	£37,306	1.470	£25,380
PR	£54,551	7.449	£0	0.000	£0

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 179. Cost-effectiveness results – Scenario analysis 4 – GT4 TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£27,836	12.671	-	-	-
BSC	£28,835	11.271	£999	-1.400	Dominated
SMV	£34,982	13.928	£7,146	1.257	£5,685
2D/3D	£37,220	14.387	£9,384	1.715	£5,471
EBR/GZR	£42,298	14.265	£14,462	1.594	£9,075
LDV/SOF	£43,747	14.387	£15,911	1.715	£9,276
DCV/PR	£57,873	14.344	£30,037	1.673	£17,956
DCV+SOF	£64,599	14.347	£36,763	1.676	£21,936

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

- **Scenario analysis 5 – regression from "SVR,F4" to "SVR,F0-F3":**

Probability of regression from "SVR,F4" to "SVR,F0-F3" based on the D'Ambrosio (0.167) et al 2012 data was implemented in the model. [162]Results are presented from Table 180 to Table 191.

Table 180. Cost-effectiveness results – Scenario analysis 5 – GT1a TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£49,574	8.844	-	-	-
SOF	£53,239	11.403	£3,665	2.558	£1,433
EBR/GZR	£54,810	12.272	£5,236	3.428	£1,527
SMV	£56,279	10.450	£6,705	1.606	£4,175
LDV/SOF	£57,195	12.272	£7,621	3.428	£2,223
2D/3D	£83,631	12.087	£34,057	3.243	£10,503

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 181. Cost-effectiveness results – Scenario analysis 5 – GT1a TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,580	13.473	-	-	-
BSC	£30,513	11.404	£3,932	-2.069	Dominated
LDV/SOF	£32,059	15.098	£5,479	1.625	£3,371
SMV	£36,693	14.550	£10,113	1.077	£9,388
2D/3D	£40,479	15.225	£13,899	1.752	£7,935
EBR/GZR	£42,389	15.150	£15,809	1.677	£9,427
SOF	£43,855	14.942	£17,275	1.469	£11,763
DCV+SOF	£64,902	15.217	£38,321	1.744	£21,976

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 182. Cost-effectiveness results – Scenario analysis 5 – GT1a TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£52,198	8.082	-	-	-
SMV	£52,327	10.584	£128	2.502	£51
EBR/GZR	£55,046	11.724	£2,848	3.642	£782
SOF	£56,207	10.477	£4,009	2.395	£1,674
LDV/SOF	£57,101	11.773	£4,903	3.691	£1,328
2D/3D	£82,514	11.751	£30,315	3.669	£8,262

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 183. Cost-effectiveness results – Scenario analysis 5 – GT1a TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£27,836	12.806	-	-	-
BSC	£28,835	11.271	£999	-1.535	Dominated
SMV	£34,982	14.203	£7,146	1.398	£5,112
2D/3D	£39,915	14.713	£12,079	1.907	£6,334
EBR/GZR	£42,298	14.578	£14,462	1.773	£8,159
LDV/SOF	£43,747	14.713	£15,911	1.907	£8,343
SOF	£45,111	14.198	£17,275	1.393	£12,403
DCV+SOF	£64,599	14.670	£36,763	1.864	£19,718

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 184. Cost-effectiveness results – Scenario analysis 5 – GT1b TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SOF	£49,502	11.984	-£540	3.212	Dominant (vs PR)
PR	£50,042	8.772	-	-	-
2D/3D	£50,796	12.429	£755	3.657	£206
EBR/GZR	£53,430	12.487	£3,388	3.715	£912
LDV/SOF	£56,177	12.431	£6,135	3.659	£1,677
SMV	£56,592	10.402	£6,551	1.630	£4,019

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 185. Cost-effectiveness results – Scenario analysis 5 – GT1b TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,800	13.442	-	-	-
BSC	£30,513	11.404	£3,713	-2.039	Dominated
LDV/SOF	£31,899	15.120	£5,099	1.678	£3,039
SMV	£37,062	14.499	£10,262	1.057	£9,710
2D/3D	£40,232	15.246	£13,432	1.804	£7,446
EBR/GZR	£41,963	15.209	£15,162	1.766	£8,585
SOF	£42,161	15.175	£15,361	1.733	£8,865
DCV+SOF	£65,018	15.201	£38,218	1.758	£21,739

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 186. Cost-effectiveness results – Scenario analysis 5 – GT1b TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SMV	£49,256	11.043	-£1,077	2.682	Dominant (vs PR)
2D/3D	£49,579	12.091	-£753	3.730	Dominant (vs PR)
PR	£50,332	8.361	-	-	-
EBR/GZR	£51,873	12.198	£1,540	3.837	£401
LDV/SOF	£54,258	12.198	£3,925	3.837	£1,023
SOF	£58,369	10.154	£8,037	1.793	£4,482

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 187. Cost-effectiveness results – Scenario analysis 5 – GT1b TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£28,407	12.730	-	-	-
BSC	£28,835	11.271	£428	-1.459	Dominated
SMV	£35,177	14.178	£6,770	1.448	£4,676
2D/3D	£38,905	14.835	£10,499	2.105	£4,988
EBR/GZR	£40,595	14.804	£12,188	2.074	£5,877
LDV/SOF	£43,060	14.804	£14,654	2.074	£7,066
SOF	£44,393	14.293	£15,987	1.564	£10,225
DCV+SOF	£63,650	14.796	£35,244	2.066	£17,060

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 188. Cost-effectiveness results – Scenario analysis 5 – GT4 TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£49,574	8.844	-	-	-
SOF	£50,770	11.787	£1,196	2.942	£406
EBR/GZR	£54,810	12.272	£5,236	3.428	£1,527
SMV	£56,279	10.450	£6,705	1.606	£4,175
LDV/SOF	£57,195	12.272	£7,621	3.428	£2,223
DCV/PR	£70,434	12.351	£20,860	3.506	£5,949
2D/3D	£79,816	12.245	£30,242	3.400	£8,894

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 189. Cost-effectiveness results – Scenario analysis 5 – GT4 TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£26,580	13.473	-	-	-
BSC	£30,513	11.404	£3,932	-2.069	Dominated
SMV	£36,693	14.550	£10,113	1.077	£9,388
2D/3D	£37,785	15.225	£11,204	1.752	£6,396
EBR/GZR	£42,389	15.150	£15,809	1.677	£9,427
DCV/PR	£58,178	15.207	£31,598	1.735	£18,217

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 190. Cost-effectiveness results – Scenario analysis 5 – GT4 TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£51,201	8.231	-	-	-
SMV	£51,737	10.672	£537	2.441	£220
EBR/GZR	£55,046	11.724	£3,845	3.493	£1,101
SOF	£56,207	10.477	£5,006	2.246	£2,229
LDV/SOF	£57,101	11.773	£5,901	3.542	£1,666
DCV/PR	£70,373	11.845	£19,172	3.614	£5,305
2D/3D	£79,699	11.754	£28,498	3.523	£8,090

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 191. Cost-effectiveness results – Scenario analysis 5 – GT4 TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£27,836	12.806	-	-	-
BSC	£28,835	11.271	£999	-1.535	Dominated
SMV	£34,982	14.203	£7,146	1.398	£5,112
2D/3D	£37,220	14.713	£9,384	1.907	£4,920
EBR/GZR	£42,298	14.578	£14,462	1.773	£8,159
LDV/SOF	£43,747	14.713	£15,911	1.907	£8,343
DCV/PR	£57,873	14.664	£30,037	1.859	£16,160
DCV+SOF	£64,599	14.670	£36,763	1.864	£19,718

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

- **Scenario analysis 6 – varying the time horizon of the model:**
  - 5 years

Table 192. Cost-effectiveness results – Scenario analysis 6 – GT1a TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£19,691	2.438	-	-	-
SMV	£34,917	2.573	£15,226	0.134	£113,537
SOF	£37,056	2.629	£17,365	0.191	£90,942
EBR/GZR	£42,785	2.698	£23,094	0.259	£89,002
LDV/SOF	£45,171	2.698	£25,479	0.259	£98,191
2D/3D	£70,427	2.685	£50,736	0.247	£205,703

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained;; QALYs, quality-adjusted life years

Table 193. Cost-effectiveness results – Scenario analysis 6 – GT1a TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£3,275	3.222	£9,065	0.046	£195,903 (PR vs)
PR	£12,340	3.268	-	-	-
LDV/SOF	£28,526	3.505	£16,186	0.236	£68,532
SMV	£29,444	3.418	£17,104	0.149	£114,583
2D/3D	£37,677	3.510	£25,337	0.242	£104,886
EBR/GZR	£39,099	3.504	£26,759	0.236	£113,422
SOF	£39,427	3.458	£27,087	0.190	£142,655
DCV+SOF	£62,099	3.502	£49,759	0.233	£213,104

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 194. Cost-effectiveness results – Scenario analysis 6 – GT1a TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£19,756	2.403	-	-	-
SMV	£33,615	2.579	£13,859	0.176	£78,551
SOF	£37,267	2.599	£17,511	0.196	£89,414
EBR/GZR	£42,349	2.690	£22,592	0.288	£78,538
LDV/SOF	£44,660	2.693	£24,904	0.290	£85,775
2D/3D	£69,689	2.688	£49,933	0.285	£175,130

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 195. Cost-effectiveness results – Scenario analysis 6 – GT1a TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£3,374	3.216	£8,630	0.007	£1,212,681 (PR vs)
PR	£12,004	3.223	-	-	-
SMV	£28,781	3.397	£16,778	0.174	£96,401
2D/3D	£37,100	3.497	£25,096	0.274	£91,530
EBR/GZR	£38,579	3.486	£26,575	0.263	£100,983
SOF	£39,065	3.425	£27,061	0.202	£134,012
LDV/SOF	£40,932	3.497	£28,928	0.274	£105,518
DCV+SOF	£61,551	3.486	£49,547	0.263	£188,192

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years; QALYs, quality-adjusted life years

Table 196. Cost-effectiveness results – Scenario analysis 6 – GT1b TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£19,781	2.435	-	-	-
SMV	£34,983	2.570	£15,202	0.135	£112,678
SOF	£36,227	2.659	£16,446	0.224	£73,412
2D/3D	£39,576	2.706	£19,795	0.271	£73,038
EBR/GZR	£42,482	2.709	£22,701	0.274	£82,981
LDV/SOF	£44,947	2.706	£25,166	0.271	£92,962

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 197. Cost-effectiveness results – Scenario analysis 6 – GT1b TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£3,275	3.222	£9,084	0.044	£204,799 (PR vs)
PR	£12,359	3.267	-	-	-
LDV/SOF	£28,509	3.506	£16,150	0.240	£67,354
SMV	£29,479	3.414	£17,120	0.148	£116,016
2D/3D	£37,570	3.512	£25,211	0.245	£102,875
EBR/GZR	£39,056	3.509	£26,697	0.242	£110,203
SOF	£39,254	3.476	£26,895	0.209	£128,492
DCV+SOF	£62,111	3.501	£49,752	0.234	£212,426

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 198. Cost-effectiveness results – Scenario analysis 6 – GT1b TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£19,391	2.416	-	-	-
SMV	£32,956	2.603	£13,565	0.187	£72,483
SOF	£37,757	2.581	£18,366	0.165	£111,153
2D/3D	£38,809	2.711	£19,418	0.295	£65,809
EBR/GZR	£41,638	2.716	£22,247	0.300	£74,060
LDV/SOF	£44,023	2.716	£24,632	0.300	£81,997

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 199. Cost-effectiveness results – Scenario analysis 6 – GT1b TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£3,374	3.216	£8,682	0.002	£4,552,946 (PR vs)
PR	£12,056	3.218	-	-	-
SMV	£28,802	3.395	£16,746	0.177	£94,474
2D/3D	£36,908	3.507	£24,852	0.289	£85,905
EBR/GZR	£38,391	3.504	£26,335	0.287	£91,824
SOF	£38,986	3.432	£26,930	0.215	£125,310
LDV/SOF	£40,857	3.504	£28,800	0.287	£100,421
DCV+SOF	£61,447	3.496	£49,390	0.279	£177,182

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 200. Cost-effectiveness results – Scenario analysis 6 – GT4 TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£19,691	2.438	-	-	-
SMV	£34,917	2.573	£15,226	0.134	£113,537
SOF	£36,509	2.649	£16,818	0.211	£79,815
EBR/GZR	£42,785	2.698	£23,094	0.259	£89,002
LDV/SOF	£45,171	2.698	£25,479	0.259	£98,191
DCV/PR	£58,827	2.637	£39,136	0.199	£196,878
2D/3D	£67,391	2.692	£47,700	0.254	£187,758

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 201. Cost-effectiveness results – Scenario analysis 6 – GT4 TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£3,275	3.222	£9,065	0.046	£195,903 (PR vs)
PR	£12,340	3.268	-	-	-
SMV	£29,444	3.418	£17,104	0.149	£114,583
2D/3D	£34,982	3.510	£22,642	0.242	£93,745
EBR/GZR	£39,099	3.504	£26,759	0.236	£113,422
DCV/PR	£55,395	3.439	£43,054	0.171	£252,046

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 202. Cost-effectiveness results – Scenario analysis 6 – GT4 TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£19,561	2.410	-	-	-
SMV	£33,488	2.584	£13,927	0.174	£80,019
SOF	£37,267	2.599	£17,706	0.189	£93,720
EBR/GZR	£42,349	2.690	£22,788	0.281	£81,168
LDV/SOF	£44,660	2.693	£25,099	0.283	£88,557
DCV/PR	£58,303	2.632	£38,743	0.222	£174,130
2D/3D	£66,863	2.688	£47,302	0.278	£170,127

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 203. Cost-effectiveness results – Scenario analysis 6 – GT4 TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£3,374	3.216	£8,630	0.007	£1,212,681 (PR vs)
PR	£12,004	3.223	-	-	-
SMV	£28,781	3.397	£16,778	0.174	£96,401
2D/3D	£34,405	3.497	£22,401	0.274	£81,714
EBR/GZR	£38,579	3.486	£26,575	0.263	£100,983
LDV/SOF	£40,932	3.497	£28,928	0.274	£105,518
DCV/PR	£54,840	3.423	£42,836	0.200	£213,724
DCV+SOF	£61,551	3.486	£49,547	0.263	£188,192

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

- 10 years

Table 204. Cost-effectiveness results – Scenario analysis 6 – GT1a TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£29,690	4.260	-	-	-
SMV	£42,903	4.492	£13,212	0.232	£56,986
SOF	£43,829	4.601	£14,138	0.341	£41,517
EBR/GZR	£48,479	4.729	£18,789	0.469	£40,033
LDV/SOF	£50,865	4.729	£21,174	0.469	£45,119
2D/3D	£76,341	4.713	£46,651	0.453	£103,054

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 205. Cost-effectiveness results – Scenario analysis 6 – GT1a TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£7,439	5.683	£6,800	0.262	£25,933 (PR vs)
PR	£14,240	5.946	-	-	-
LDV/SOF	£28,769	6.338	£14,530	0.392	£37,033
SMV	£30,280	6.203	£16,040	0.257	£62,324
2D/3D	£37,801	6.356	£23,561	0.411	£57,334
EBR/GZR	£39,302	6.343	£25,062	0.398	£62,991
SOF	£39,815	6.280	£25,576	0.334	£76,484
DCV+SOF	£62,223	6.348	£47,983	0.403	£119,097

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 206. Cost-effectiveness results – Scenario analysis 6 – GT1a TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£30,686	4.200	-	-	-
SMV	£41,124	4.543	£10,438	0.343	£30,403
SOF	£44,941	4.541	£14,255	0.341	£41,767
EBR/GZR	£48,379	4.725	£17,693	0.525	£33,716
LDV/SOF	£50,624	4.731	£19,938	0.531	£37,547
2D/3D	£75,672	4.732	£44,987	0.532	£84,494

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 207. Cost-effectiveness results – Scenario analysis 6 – GT1a TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£7,637	5.686	£6,759	0.186	£36,301 (PR vs)
PR	£14,396	5.873	-	-	-
SMV	£29,580	6.197	£15,184	0.324	£46,843
2D/3D	£37,314	6.346	£22,918	0.473	£48,458
EBR/GZR	£38,952	6.320	£24,556	0.447	£54,895
SOF	£39,848	6.221	£25,452	0.348	£73,043
LDV/SOF	£41,147	6.346	£26,751	0.473	£56,563
DCV+SOF	£61,807	6.331	£47,411	0.458	£103,449

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 208. Cost-effectiveness results – Scenario analysis 6 – GT1b TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£29,877	4.252	-	-	-
SOF	£42,260	4.670	£12,383	0.418	£29,597
SMV	£43,032	4.486	£13,155	0.234	£56,168
2D/3D	£45,072	4.748	£15,195	0.496	£30,655
EBR/GZR	£47,902	4.755	£18,025	0.503	£35,836
LDV/SOF	£50,439	4.748	£20,562	0.496	£41,436

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 209. Cost-effectiveness results – Scenario analysis 6 – GT1b TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£7,439	5.683	£6,850	0.257	£26,616 (PR vs)
PR	£14,290	5.941	-	-	-
LDV/SOF	£28,729	6.342	£14,440	0.401	£36,001
SMV	£30,369	6.194	£16,079	0.254	£63,406
2D/3D	£37,671	6.360	£23,381	0.420	£55,730
EBR/GZR	£39,196	6.354	£24,907	0.413	£60,310
SOF	£39,395	6.321	£25,105	0.380	£66,069
DCV+SOF	£62,252	6.346	£47,962	0.405	£118,444

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 210. Cost-effectiveness results – Scenario analysis 6 – GT1b TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£29,928	4.233	-	-	-
SMV	£39,837	4.600	£9,909	0.367	£26,963
2D/3D	£44,345	4.771	£14,417	0.538	£26,775
SOF	£45,865	4.500	£15,937	0.267	£59,672
EBR/GZR	£47,028	4.785	£17,099	0.552	£30,960
LDV/SOF	£49,413	4.785	£19,485	0.552	£35,281

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 211. Cost-effectiveness results – Scenario analysis 6 – GT1b TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£7,637	5.686	£6,898	0.173	£39,873 (PR vs)
PR	£14,535	5.859	-	-	-
SMV	£29,630	6.192	£15,095	0.333	£45,391
2D/3D	£36,979	6.369	£22,443	0.509	£44,069
EBR/GZR	£38,498	6.363	£23,963	0.503	£47,598
SOF	£39,657	6.239	£25,121	0.380	£66,157
LDV/SOF	£40,964	6.363	£26,428	0.503	£52,496
DCV+SOF	£61,554	6.355	£47,018	0.495	£94,910

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 212. Cost-effectiveness results – Scenario analysis 6 – GT4 TN C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£29,690	4.260	-	-	-
SOF	£42,792	4.647	£13,102	0.387	£33,885
SMV	£42,903	4.492	£13,212	0.232	£56,986
EBR/GZR	£48,479	4.729	£18,789	0.469	£40,033
LDV/SOF	£50,865	4.729	£21,174	0.469	£45,119
DCV/PR	£64,313	4.689	£34,623	0.429	£80,648
2D/3D	£73,100	4.732	£43,409	0.472	£92,048

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 213. Cost-effectiveness results – Scenario analysis 6 – GT4 TN NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£7,439	5.683	£6,800	0.262	£25,933 (PR vs)
PR	£14,240	5.946	-	-	-
SMV	£30,280	6.203	£16,040	0.257	£62,324
2D/3D	£35,106	6.356	£20,866	0.411	£50,778
EBR/GZR	£39,302	6.343	£25,062	0.398	£62,991
DCV/PR	£55,514	6.292	£41,275	0.346	£119,175

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 214. Cost-effectiveness results – Scenario analysis 6 – GT4 TE C

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
PR	£30,281	4.218	-	-	-
SMV	£40,877	4.554	£10,596	0.337	£31,471
SOF	£44,941	4.541	£14,660	0.324	£45,284
EBR/GZR	£48,379	4.725	£18,098	0.507	£35,682
LDV/SOF	£50,624	4.731	£20,343	0.513	£39,620
DCV/PR	£64,069	4.690	£33,789	0.473	£71,489
2D/3D	£72,842	4.733	£42,561	0.516	£82,549

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 215. Cost-effectiveness results – Scenario analysis 6 – GT4 TE NC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
BSC	£7,637	5.686	£6,759	0.186	£36,301 (PR vs)
PR	£14,396	5.873	-	-	-
SMV	£29,580	6.197	£15,184	0.324	£46,843
2D/3D	£34,620	6.346	£20,224	0.473	£42,762
EBR/GZR	£38,952	6.320	£24,556	0.447	£54,895
LDV/SOF	£41,147	6.346	£26,751	0.473	£56,563
DCV/PR	£55,090	6.274	£40,694	0.401	£101,442
DCV+SOF	£61,807	6.331	£47,411	0.458	£103,449

Abbreviations. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

5.8.4 Summary of sensitivity analyses results

The probabilistic sensitivity analysis results support the deterministic analysis results. Compared to PR, EBR/GZR is consistently a cost-effective option for the treatment of HCV patients in every subpopulation with ICERs falling well below the £20,000 threshold.

Deterministic sensitivity analyses of EBR/GZR against PR for all subpopulations demonstrated that the inputs that most affect the ICERs are the cirrhotic health state utility value, the relative risk of PR, the EZR/EBR weekly drug cost and patients' age at baseline. Varying the discount rates of QALYs and costs has showed to substantially impact the ICERs.

Scenario analyses showed that the cost-effectiveness of EBR/GZR is robust to the sources and structural uncertainty assessed, including: naïve comparison efficacy and safety estimates, implementation of GT4 specific dataset, age-dependent transition probabilities and liver fibrosis regression in cirrhotic patients who have achieved SVR.

5.9 Subgroup analysis

5.9.1 Types of subgroups that are not considered relevant

Analyses on the subgroups of patients with chronic HCV are presented in sections 5.7 and 5.8.

5.9.2 Analysis of subgroups

See above.

5.9.3 Definition of the characteristics of patients in the subgroup

See above.

5.9.4 Description of how the statistical analysis was carried out

See above.

5.9.5 Results of subgroup analyses

See above.

5.9.6 Identification of any obvious subgroups that were not considered

See above.

5.10 Validation

5.10.1 Methods used to validate and quality assure the model

Clinical benefit

Expert validation

The model approach and inputs have been validated by an external health economist with expertise in hepatitis C. This individual was selected as a leading expert in health economics practice and methodology development in the UK for the economic evaluation of HCV. The methods and key assumptions regarding the model structure, subgroups and comparators, the analysis of clinical inputs (SVR, discontinuation and AE rates) and HRQoL undertaken, the health state utility values and the resource use and costs used in the economic model were all discussed.

As discussed in section 5.2 the structure of the model is based on the Hartwell et al 2011[26] and Shepherd et al 2007 [111] models that were implemented in previous HCV HTA submissions recommended by NICE.

The accuracy of the implementation and programming of the model was verified via internal quality control processes using an internal quality control checklist, available in Appendix 23.

5.11 Interpretation and conclusions of economic evidence

5.11.1 Comparison with published economic literature

Only one conference abstract assessing the cost-effectiveness of EBR/GZR was identified from the SLR. [163] However, this study explored the health and economic impact of EBR/GZR treatment on CKD patients infected with chronic HCV from a U.S. perspective. It is therefore not appropriate to compare the results of the cost-effectiveness analysis in this submission with the results of the published abstract.

5.11.2 Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation was consistent with the GT1 and GT4 chronic HCV population eligible for EBR/GZR as per the anticipated licence. As mentioned previously (see section 5.3.1), all EBR/GZR trials, which assessed patients in line with the anticipated licenced indication, were used in the model.

5.11.3 Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in EBR/GZR trials and the de novo economic evaluation are reflective of GT1 and GT4 patients with chronic HCV in the UK.
- The cost-effectiveness model is consistent with previous models in the published literature and previous HCV submissions to NICE.
- The resource utilisation and unit costs are reflective of those in UK clinical practice and were mainly derived from the published literature and previous NICE submissions
- All assumptions used in the model were validated by UK clinical experts

5.11.4 Strengths and weaknesses of the evaluation

Strengths:

- The cost-effectiveness analysis makes use of the best available evidence to inform the model.
- The economic model is consistent with previous models assessed by NICE and the published literature. The majority of the inputs selected were considered appropriate by NICE in previous CE analyses and have also been validated by clinicians and a health economist expert in the HCV area.
- MSD is the first manufacturer to present the findings of a NMA comparing their product relative to recently approved DAA regimens. This novel NMA methodology uses imputed PR simulation arms to enable comparisons, and also incorporates the C-EDGE H2H clinical trial, which compares EBR/GZR to SOF+PR. The results of the NMA were also supported by the findings of a naïve comparison suggesting that the all-DAA regimens are broadly comparable.
- The probability of re-infection in patients who achieve SVR has been included in the base case analysis in order to better reflect the epidemiology of the disease. Additionally, the initial findings of fibrosis regression due to achieving SVR have been explored in scenario analysis.
- HRQoL data from EBR/GZR clinical trials were implemented in sensitivity analysis to explore the uncertainty around selected utility inputs.

Limitations:

- Sequential treatment, following patient's treatment failure with one of the latest DAAs, was not modelled as no DAA is licensed for use in this way.

- Related to the lack of comparator data, several assumptions were required in order to facilitate the comparison against the second-generation DAAs in terms of efficacy and safety data, described in section 5.6.3.
- Efficacy and safety data for GT4 patients are limited due to small patient numbers included in the EBR/GZR and comparator trials.
- The cost-effectiveness model has been populated with historical data reflective of the clinical pathway of patients treated with IFN-based regimens as no evidence is available that reflect the IFN-free care pathway.

5.11.5 Further analyses

Observational data on re-infection rates and regression of liver fibrosis following achievement of SVR would be useful to reinforce the limited data that are available.

6 Assessment of factors relevant to the NHS and other parties

6.1 Analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness

Not applicable

6.2 Number of people eligible for treatment in England

The number of GT1 and GT4 patients eligible for treatment in England was estimated based on the approach adopted in the latest NICE costing template for the new DAAs.[9] The steps followed are explained below:

- In the latest HCV report published by PHE, it was estimated that approximately 0.4% of the adult population in England are infected with HCV. [8] This percentage was applied to the England adult population estimates which were calculated by using the most recent England population estimate [164] and applying the ONS projected growth rate. [164]
- The proportion of diagnosed population (52%) and the proportion of those eligible for treatment (28.5%) were further applied. (NICE costing template) Since EBR/GZR is only licenced for the treatment of GT1 and GT4 chronic HCV patients, approximately 50% of the aforementioned patients will be eligible for treatment with this regimen.[165]
- Finally, the average transition rate to treatment was applied based on the estimates published in the NICE costing template, which were estimated from the treatment rate assumptions adopted in the manufacturer submission in TA365. For 2016, this equates to approximately 30.54% while an assumption was made that it will increase to approximately 59% by 2021.

Table 216 summarises the steps followed to estimate the number of GT1 and 4 patients eligible for treatment with EBR/GZR.

Table 216. Estimated patient numbers eligible for treatment in England

Parameters	Estimate	2016 Year 0	2017 Year 1	2018 Year 2	2019 Year 3	2020 Year 4	2021 Year 5	Source
Adult population of England (18+)		43,432,783	43,088,079	43,432,783	43,761,450	44,092,604	44,411,034	ONS Mid-2014 UK population estimates [164]
Prevalence of CHC	0.40%	173,731	172,352	173,731	175,046	176,370	177,644	PHE 2015 report [8]
Proportion of people diagnosed	52.00%	90,340	89,623	90,340	91,024	91,713	92,375	NICE costing template [9]
Proportion of people eligible for treatment	28.49%	25,734	25,530	25,734	25,929	26,125	26,314	NICE costing template [9]
Proportion of GT1 and GT4 patients	50.30%	12,944	12,842	12,944	13,042	13,141	13,236	PHE 2013 report[165]
Number of HCV patients to be treated								
Average annual transition rate to treatment		30.54%	39.29%	45.84%	52.39%	58.94%	58.94%	NICE costing template [9]
Total number of GT1 and GT4 patients to be treated		**3,953**	**5,046**	**5,934**	**6,833**	**7,745**	**7,801**	NICE costing template [9]

6.3 Assumptions that were made about current treatment options and uptake of technologies

With the implementation of NICE guidance for the new DAAs (i.e. TA363, TA364, TA365), the treatment pathway has been simplified; as IFN-free regimens require less monitoring vs older agents. NHSE acknowledges the impact of the new DAA treatment options available, and has confirmed that treatment uptake will reach ~10,000 patients by 2017. [50] Assuming that GT1 & GT4 represent approximately 50% of chronic HCV patients, the number of patients to be treated is in line with the projections of NHSE (see Table 216, section 6.2)

Historically, prescribing has followed the NHSE CCP. However, since April 2016 prescribing is dictated by implementation of NICE TAs through CQUIN scheme. This framework prioritises treatment for people with the highest unmet clinical need, recommending treatment options at the lowest acquisition cost, which is based on annual regional tendering frameworks.[11-13, 50]

All assumptions adopted above are believed to reflect the current HCV environment; however, the treatment landscape is rapidly evolving. This makes it challenging to predict any changes in terms of future treatment options and the uptake of technologies.

6.4 Assumptions that were made about market share in England

Table 217 below summarises the market shares of treatment options in the last 12 months (March 2015 - February 2016) based on sales. Unfortunately, it is not possible to distinguish further in terms of GT, and in terms of treatment regimens administered in combination with SOF, PEG or RBV. Thus, market shares of regimens recommended for genotypes falling outside of the scope of this submission are included in the table below.

Table 217 Market shares for currently available treatment options from March 2015.

Regimen	Market shares (March 2015 - February 2016)
PEG	5%
RBV	4%
SMV	5%
SOF	32%
DCV	11%
LDV/SOF	36%
3D/2D	7%

Abbreviations. 3D/2D, ombitasvir/paritaprevir/ritonavir ± dasabuvir; DCV, daclatasvir; LDV, ledipasvir; PEG, peginterferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir;

For the reasons outlined in section 6.3 above, it is difficult to predict the future market shares of these treatment options and any possible uptake of EBR/GZR.

6.5 Other significant costs associated with treatment that may be of interest to commissioners

There are no other significant costs associated with EBR/GZR treatment regimen that differ significantly from the currently available IFN-free treatment options and could impact the budget of commissioners.

6.6 Unit costs assumed and how they were calculated

All unit costs considered in this section were based upon the drug costs included in the relevant section (Section 5.5) of the submission document.

The unit cost of EBR/GZR pack of 28 tablets is £12,166.67.

6.7 Estimates of resource savings

All available new DAA regimens incur similar monitoring costs, which are cost-saving when compared to older regimens administered in combination with PEG/IFN. This is due to the safety and tolerability profile of the IFN-free regimens, any discontinuations, and any AEs due to the toxicity of the regimens can be avoided.

6.8 State the estimated annual budget impact on the NHS in England.

There is no additional budget impact anticipated with the introduction of EBR/GZR given the defined DAA budget for treatment of patients with HCV in England.

It is MSD's understanding that the entire annual NHSE HCV budget will be used for the treatment of patients. Thus, as verbally confirmed by Claire Foreman (Specialised Services Regional Programme of Care Manager) during the British viral hepatitis group (BVHG) March 2016 meeting held at the Royal College of Physicians in London, any decrease in treatment costs should result in an increase in the number of patients being treated.[166]

6.9 Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

Not applicable.

6.10 Highlight the main limitations within the budget impact analysis.

Any benefits to the society from avoiding onwards transmission of the disease to general population were not incorporated in the analysis.

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Single technology appraisal

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

Dear [redacted],

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 22 April 2016 from Merck Sharp & Dohme. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Monday 6 June 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Helen Tucker, Technical Lead (Helen.Tucker@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Literature searching

A1. **Priority question**: Please explain why search terms for peginterferon alfa and ribavirin were not included in the clinical effectiveness search strategies (Section 4.1.2; Appendix 2), when peginterferon alfa with ribavirin is listed as a comparator (page 20 of the Company Submission).

A2. Please provide the search terms used for the identification of clinical effectiveness studies from the American Association for the Study of Liver Diseases conference (Section 4.1.2; Appendix 2), and for the identification of cost-effectiveness studies from all five of the conference proceedings searched (Section 5.1.1; Appendix 12).

A3. Please provide details of the date range of databases searched for HRQoL data (Section 5.4.3; Appendix 15).

A4. Please provide details of the search terms used to search the Tufts Cost-effectiveness Analysis Registry for cost-effectiveness studies (Section 5.1.1; Appendix 12), HRQoL data (Section 5.4.3; Appendix 15) and resource identification, measurement and valuation studies (Section 5.5.2; Appendix 19).

Clinical Effectiveness

A5. **Priority question**: Please provide all sustained virologic response (SVR) results (number with SVR and number of patients in each arm) for all treatment arms for all included RCTs, that is, not only the studies used in the network meta-analysis. If N=0, please include this.

A6. **Priority question**: Please provide the adverse event rates for overall adverse events, discontinuation due to adverse events, anaemia, nausea, neutropenia, pruritus, and rash. For each of these, provide the number of events and number of patients in each arm for all treatment arms for all included RCTs.

A7. **Priority question**: Please provide the following:

a. All results (SVR and AEs) for the 12 subgroups (that is, by genotype, treatment history and cirrhosis status) for all treatment arms for the MSD studies.

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b. All SVR results for the 4 subgroups as defined for the network meta-analysis of AEs (that is, GT1, with/without cirrhosis; and GT4, with/without cirrhosis) for the MSD studies.

A8. **Priority question**: The WinBUGS code used for the network meta-analysis was provided but the corresponding data are missing.

a. Please provide the data used in each network meta-analysis and highlight which control arms have been imputed as reported in Section 4.10.12 of the company submission.

b. Please also provide details of how the data were imputed for any missing comparator arms (e.g., full poster and the technical report for the analyses presented at ISPOR 2015 Milan [reference 106 in the company submission], statistical codes and data inputs used in creating the imputation as well as the outputs).

A9. In table 35 (pages 124 to 125 of the company submission), the trials included in the network meta-analysis of sustained viral response are listed.

a. Please explain why the ATOMIC, ION-1, PEARL-3, ELECTRON, LONESTAR, Mizokami and PEARL-1 trials are not included for GT1a/TX-Naive/No Cirrhosis (for instance: ATOMIC matches the inclusion criteria more closely than ALLY-2).

b. Please explain why the Sulkowski, ADVANCE, ALLY-2, ATOMIC, ELECTRON, LONESTAR, PEARL-1 and Merck PN077 trials are not included for GT1a/TX-Naive/With Cirrhosis (for instance: ALLY-2 was included for "GT1a/TX-Naive/No Cirrhosis", but patients with mixed fibrosis status were included, so it could also be included here. The same applies to PN077).

c. Please provide the selection criteria for inclusion in all network meta-analyses for sustained viral response and adverse events.

A10. Please explain why the genotypes for the network meta-analysis of sustained viral response are split by subtype into GT1a and GT1b.

A11. Please provide full references and PDF documents for the following citations in the table of included studies in appendix 3.

10	Gane et al.	2013	Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis c
12	Hézode et al.	2014	Daclatasvir in Combination With Peginterferon Alfa-2a and Ribavirin for Treatment-Naive Patients With HCV Genotype 4 Infection: Phase 3 COMMAND-4 Results

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14	Jacobson et al.	2011	Telaprevir for previously untreated chronic hepatitis c virus infection
22	Lawitz et al.	2013	Sofosbuvir for previously untreated chronic hepatitis c infection
45	Sulkowski et al.	2014	Daclatasvir plus sofosbuvir for previously treated or untreated chronic hcv infection

A12. **Priority question**: Table 69 (page 201 of the company submission): Please provide full HRQoL results for the elbasvir/grazoprevir comparative studies (C-CO-STAR, C-EDGE TN, C-SURFER and C-EDGE H2H), that is, baseline data, 12-week data, and change score (N, mean and SD) for all treatment arms, and a measure of the significance of the difference between arms (p-value or 95% CI).

Section B: Clarification on cost-effectiveness data

Literature searching

B1. In the final scope, the related NICE guidelines are listed as TA 75, TA 106, TA 200, TA 252, TA 253, TA 330, TA 331, TA 363, TA 364 and TA 365. However, in the summary list for identified UK cost-effectiveness studies (table 58, page 159 of the company submission), only TA 252, TA 253, TA 363, TA 364, TA 365 and TA 330 were included. Please explain why TA 75, TA 106, TA 200 and TA 331 were not included.

B2. Please explain why the Scottish Medicine Consortium (SMC) assessment reports for the new treatments in Chronic Hepatitis C had not been identified in Table 58.

B3. In Table 58, for the Shepherd et al. 2005 study, the overall ICER estimate is higher than all other subgroup ICER estimates. It is expected that the overall ICER estimate would be within the boundaries of the minimum and maximum ICER estimates from the subgroups. Please check whether this is correct.

B4. The information presented in table 58 for the Wright et al. 2006 and the Grieve et al. 2006 studies appears the same. Please confirm if these are 2 publications of the same cost-effectiveness analysis.

Population

B5. **Priority request:** The subgroups listed below were included in the NICE final scope as clinically important subgroups for this treatment. Please reconsider whether it would be useful to provide some or all of these analyses (taking into account the anticipated indication in the SmPC and the appraisal committee considerations of previous Hep C topics), otherwise please provide further justification for not providing these analyses.

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- People with renal impairment
- People co-infected with HIV
- People with advanced liver disease
- Post-liver transplantation
- People with haemoglobinopathies
- People who are intolerable to and ineligible for IFN treatment

B6. Treatment experienced patients considered in the economic analyses include patients who are non or partial responders and people with relapsed disease. Chronic hepatitis C treatments may have different effectiveness for each of these subgroups. Please consider exploring the impact of response to previous treatment in subgroup analyses or provide justification why this may not be appropriate.

B7. Treatment experienced patients in the economic analyses may include direct acting antiviral (DAA) naïve or DAA experienced patients. Elbasvir/grazoprevir and its comparators may have different effectiveness for DAA naïve and DAA experienced patients.

a. Please provide information on how many of the treatment experienced patients had used DAA before trial inclusion and how many had used non-DAA treatments, for example peginterferon alfa.

b. Please consider exploring the impact of type of previous treatment (DAA versus non-DAA treatment) in subgroup analyses or provide justification why this may not be appropriate.

Model Structure

B8. Figure 16 (page188 of the company submission): There should be no connection possible between F4 and (SVR, F0-F3) states. Please confirm this and provide a corrected version of Figure 16.

B9. In the model, patients in SVR F1, SVR F2 and SVR F3 states relapse only to F0 and not to F1, F2 and F3, thus implying that the liver damage caused by chronic hepatitis C is fully reversible. Please justify this assumption.

B10. Please justify the modelling assumption that there is no progression to more severe health states while patients are on treatment.

B11. In the model, it is assumed that all transition probabilities except for sustained virological response, discontinuation and adverse events rates, were identical for all considered chronic hepatitis C treatments.

a. Please justify this assumption that chronic hepatitis C treatment has no effect on disease progression.

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b. Also please justify the assumption that the disease progression probabilities are the same between different subgroups (treatment naïve vs treatment experienced; genotypes 1a, 1b and 4).

Intervention/Comparator

B12. **Priority request:** Appendix 1 of the company submission states that the treatment duration for elbasvir/grazoprevir might be increased to 16 weeks with ribavirin at the discretion of physicians. Please provide an estimate of the proportion of patients that would receive this longer duration of treatment with ribavirin.

B13. **Priority request:** Boceprevir and telaprevir are included as comparators of elbasvir/grazoprevir in the NICE final scope. We note that these comparators have not been included in the company submission on the basis that they are no longer considered current clinical practice. Please reconsider if it is suitable to present analyses using these comparators.

Clinical parameters and variables

B14. **Priority request:** Please describe the methodology used in obtaining the expert opinion for all the clinical assumptions in the model: for example the area of expertise, the reason for only approaching 2 experts, the set of questions posed to the experts during the face-to-face meeting and tele-conference and the individual responses of the two experts.

B15. In the SVR network meta-analysis results for GT1b patients (table 65, page 196), it can be seen that 100% of the patients achieved SVR with elbasvir/grazoprevir, even though in the discontinuation network meta-analysis results for GT1b patients (Table 66, page 197), it can be seen that some of the GT1b patients on elbasvir/grazoprevir had discontinued treatment. This implies that a patient who discontinues treatment may still achieve SVR.

a. Please justify this assumption.

b. Please also explain if all network meta-analyses (SVR, discontinuation, AEs) use the same ad-hoc analysis data type (e.g. Intention to treat, discontinuation= treatment failure).

B16. Tables 65 to 67, pages 196 to 198 of the company submission: Please provide confidence intervals in addition to the standard errors for the network meta-analyses results (relative risks of adverse events, discontinuation and SVR rates) for the treatments listed in the tables.

Utilities

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B17. **Priority request:** Utilities derived from the clinical trials (Table 70 and Table 71) are comparable to the quality of life values from the general population (Table 74). Furthermore, the utilities found in the Wright study, which are used in the base case analyses (Table 75), are substantially lower.

a. Please provide an explanation for this difference.

b. Please provide the rationale for the choice of the utility data from Wright et al (2006), apart from the fact that it was used in previous health technology appraisals.

c. Please clarify why data from 2006 can be considered to be representative for the current patient population in the UK.

B18. **Priority request:** The 3L crosswalk algorithm (page 204) was developed as an interim method to value EQ-5D-5L health states, in the absence of a UK value set. The value set for the EQ-5D-5Lis now available and published and it was shown that there is a relevant and significant difference in the range of the utility scale attainable between the 3L and the 5L. Therefore, please provide the updated model results using the utility estimates based on the EQ-5D-5L tariff as developed by Devlin et al. (2016), rather than the 3L crosswalk algorithm.

B19. **Priority request:** Page 203 of the company submission: The derivation of the utility decrements from adverse events was described as follows: "*The impact of any AEs on patients' HRQoL was captured in EQ-5D data as part of the change from baseline. To account for any improvement in HRQoL that may have occurred as a result of treatment response, the utility decrement related to AEs has been derived as the difference between baseline and the mean utility values at week 4 and end-of-treatment. An overall utility decrement of 0% was reported across all patients in the EBR/GZR trials.*"

- It is not clear how these values are generated. Please provide further clarification of the method used to derive the utility decrements due to adverse events and provide a justification for this approach.

B20. Page 244 of the company submission: Please clarify the rationale for using age-dependent utility decrements in a linear way, given that the EQ-5D data is based on questionnaires filled by patients representing a wide range of ages, thus already incorporating the impact of age. Please clarify how double counting of the impact of age is avoided in the submission.

Costs

B21. Page 226 of the company submission: Costs for outpatient visits, inpatient care, tests and investigations have been included in the model. Please clarify whether this

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captures all relevant resource use. For example, clarify whether patients use allied health care, GP visits, other medication or home care.

Results

B22. Please comment on the observed differences in clinical and economic outcomes between elbasvir/grazoprevir and other DAAs, as it was stated that there was no significant difference between DAAs and elbasvir/grazoprevir in the clinical effectiveness section of the company submission.

B23. Section 5.8.3 of the company submission: Please provide further interpretation of the scenario analyses to accompany the tables of results and figures provided. For example, please explain what drives the presented results, that is, through which mechanisms certain input changes influence the outcomes.

Model Validation

B24. Appendix 23 of the company submission: It is stated that that health economics expert validation and computerized model validation had been conducted. No details of the expert validation were provided. Please provide the details of this validation exercise, and also provide a completed version of the checklist in Appendix 23.

B25. Please consider conducting additional validation of the model (such as cross-validation, validation against external data, validation against internal data, clinical expert face validation).

Section C: Textual clarifications and additional points

C1. Table 1, page 20 of the company submission: Please explain what the term “OTVF” stands for.

C2. Page 39 of the company submission. Please provide a reference for the following statement: “*If left untreated a patients’ deteriorating QoL could also have a negative impact on carers.”*

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1st June 2016

Dear Helen,

Re. Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

The responses to the ERG clarification questions are provided below.

Should you or the ERG require any further clarification please let me know and we'll do our best to respond.

Best regards,

[redacted]

Section A: Clarification on effectiveness data

Literature searching

A1. **Priority question**: Please explain why search terms for peginterferon alfa and ribavirin were not included in the clinical effectiveness search strategies (Section 4.1.2; Appendix 2), when peginterferon alfa with ribavirin is listed as a comparator (page 20 of the Company Submission).

The clinical effectiveness search strategies were informed by the chosen methodology for the indirect treatment comparison i.e. network meta-analysis with imputed controls. Peginterferon alfa with ribavirin (PR) was selected as the most suitable treatment to base the imputation on, as it is the most commonly used active control in trials of the newer direct acting antiviral (DAA) treatments. The statistical analysis plan restricted the PR data used in the imputation of controls for each NMA to comparative trials featuring a PR arm and at least one other intervention of interest. The rationale for this was that these trials would be balanced in terms of effect modifiers for regimens containing interferon, but that may not influence outcomes for all DAA regimens. As a result, it was not necessary to identify trials where PR was the primary intervention.

A2. Please provide the search terms used for the identification of clinical effectiveness studies from the American Association for the Study of Liver Diseases conference (Section 4.1.2; Appendix 2), and for the identification of cost-effectiveness studies from all five of the conference proceedings searched (Section 5.1.1; Appendix 12).

MSD apologises for the lack of clarity. As reported on page 62 of appendix 2, the American Association for the Study of Liver Diseases annual conferences (AASLD) were searched for years 2014 and 2015. No specific search terms were applied to the 'special issues'; instead, all abstracts from relevant sessions were screened for potential eligibility. The sessions searched are included in Appendix 2 of the submission and replicated below:

Sessions searched from 2014 AASLD conference abstract booklet (Hepatology. Volume 60, Issue Supplement S1):
Parallel 6: Hepatitis C: Currently Approved Drugs
Parallel 12: Hepatitis C: New Agents -Part 1
Hepatitis Plenary
Parallel 35: Hepatitis C: New Agents - Part 2
Poster Session 2: Hepatitis C: Approved Therapeutic Agents
Poster Session 4: Hepatitis C: New Agents (Not Approved)
Poster Session 4: Hepatitis C: Preclinical Development

Sessions searched from 2015 AASLD conference abstract booklet (Hepatology. Volume 62, Issue Supplement S1):

Parallel 5: Hepatitis C: Pre-Approval Clinical Studies I
Parallel 12: Clinical and Translational Advances in Complications of Cirrhosis
Parallel 14: Hepatitis C: Approved Therapeutic Agents
Presidential Plenary: Clinical
Parallel 21: Therapeutic Interventions for Complications of Cirrhosis
Parallel 37: Hepatitis C: Pre-Approval Clinical Studies II
Poster Session 2: Hepatitis C: Therapeutics (Approved Agents)
Poster Session 4: Therapeutics: Preclinical and Early Clinical Development

A3. Please provide details of the date range of databases searched for HRQoL data (Section 5.4.3; Appendix 15).

The date range of databases searched is as follows:

- Embase database: from 1947 to 20th of January 2016

- Medline database: from 1966 to 20th of January 2016

- Cochrane database: from 1992 to 20th of January 2016

A4. Please provide details of the search terms used to search the Tufts Cost-effectiveness Analysis Registry for cost-effectiveness studies (Section 5.1.1; Appendix 12), HRQoL data (Section 5.4.3; Appendix 15) and resource identification, measurement and valuation studies (Section 5.5.2; Appendix 19).

The below table summarises the Tufts registry search terms applicable to the three searches (i.e. cost-effectiveness studies, HRQoL data, and resource identification). All the hits obtained were screened for inclusion in each of the three review types. No study design filter was applied to the search strategies in an attempt to minimise inappropriate exclusion (model/cost/resource/utility etc).

Table 1. Tufts registry searches key terms

Serial no.	Search terms	Hits	Relevant articles
1	HCV	70	0
2	Hepatitis C	112	0
3	Grazoprevir	0	0
4	Elbasvir	0	0
5	Boceprevir	8	0
6	Interferon	147	0
7	Ribavirin	62	0
8	Daclatasvir	0	0
9	Sofosbuvir	0	0
10	Ledipasvir	0	0
11	Ombitasvir	0	0
12	Paritaprevir	0	0
13	Ritonavir	20	0
14	Dasabuvir	0	0
15	Simeprevir	0	0
16	Telaprevir	6	0

Please note that all the articles found with the Tufts searches were already identified from the PubMed search.

Clinical Effectiveness

A5. **Priority question**: Please provide all sustained virologic response (SVR) results (number with SVR and number of patients in each arm) for all treatment arms for all included RCTs, that is, not only the studies used in the network meta-analysis. If N=0, please include this.

Please see the table below.

Table 1. Rates of sustained viral response in trials identified from the systematic literature review

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Jacobson et al., 2011, ADVANCE, NCT00627926	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics:	Arm 1: TVR + PR 1-12, PR 13-24 or PR 13-48	363*	271*
			Arm 2: TVR + PR 1-8, PR 9-24 or PR 9-48	364*	250*
			Arm 3: PR 1-48	361*	158*
Sulkowski et al., 2014, A1444040, NCT01359644	Open label, Randomized, Multicentre	Genotype: 1, 2, 3 Treatment history: Mixed Fibrosis status: Mixed Other characteristics:	Arm 1: SOF 1, DCV + SOF 2-24	16	14
			Arm 2: DCV + SOF 1-24	14	14
			Arm 3: DCV + SOF + R 1-24	14	12
			Arm 4: SOF 1, DCV + SOF 2-24	15	15
			Arm 5: DCV + SOF 1-24	14	14
			Arm 6: DCV + SOF + R 1-24	15	15
			Arm 7: DCV + SOF 1-12	41	41
			Arm 8: DCV + SOF + R 1-12	41	39
			Arm 9: DCV + SOF 1-24	21	21
			Arm 10: DCV + SOF + R 1-24	20	19
Poordad et al.,	Open label,	Genotype: Any	Arm 1: DCV + SOF + R 1-12	60	50

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
2015, ALLY-1, NCT02032875	Non-randomized, Multicentre	Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA viral load of ≥10,000 IU/mL	Arm 2: DCV + SOF + R 1-12	53	50
Wyles et al., 2015, ALLY-2, NCT02032888	Open label, Randomized, Multicentre	Genotype: Any Treatment history: Mixed Fibrosis status: Mixed Other characteristics: Patients with HIV-1 infection, HCV RNA ≥10,000 IU/mL	Arm 1: DCV + SOF 1-12	101	98
			Arm 2: DCV + SOF 1-8	50	38
			Arm 3: DCV + SOF 1-12	52	51
Nelson et al., 2015, ALLY-3, NCT02032901	Open label, Non-randomized, Multicentre	Genotype: 3 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥10,000 IU/mL	Arm 1: DCV + SOF 1-12	101	91
			Arm 2: DCV + SOF 1-12	51	44
Fontaine et al., 2015, ANRS HC29 BOCEPRETRANSPLANT, NCT01463956		Genotype: 1 Treatment history: Mixed Fibrosis status: Cirrhosis Other characteristics: MELD score ≤ 18; on waitlist for liver transplantation; no HIV	Arm 1: PR 1-4, BOC + PR 5-48	51*	8*
Zeuzem et al., 2014, ASPIRE, NCT00980330	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: HCV RNA level > 10,000 IU/mL,	Arm 1: SMV + PR 1-12, PR 13-48	66	46
			Arm 2: SMV + PR 1-24, PR 25-48	65	44
			Arm 3: SMV + PR 1-48	66	40
			Arm 4: SMV + PR 1-12, PR 13-48	66	44
			Arm 5: SMV + PR 1-24, PR 25-48	68	49

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
		no HIV	Arm 6: SMV + PR 1-48	65	52
			Arm 7: PR 1-48	66	15
Foster et al., 2015, ASTRAL-3, NCT02201953	Open label, Randomized, Multicentre	Genotype: 3 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 2: SOF + R 1-24	275	221
Kowdley et al., 2013, ATOMIC, NCT01329978	Open label, Randomized, Multicentre	Genotype: 1, 4, 5, 6, or indeterminate Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SOF + PR 1-12	52	47
			Arm 2: SOF + PR 1-24	125	115
			Arm 3: SOF + PR 1-12, SOF 13-24 or SOF + R 13-24	155	141
Reddy et al., 2015, ATTAIN, NCT01485991	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: HCV RNA of >10,000 IU/mL, no HIV	Arm 1: SMV + PR 1-12, PR 13-48	379	203
			Arm 2: TVR + PR 1-12, PR 13-48	384	210
Kowdley et al., 2014, AVIATOR, NCT01464827	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Mixed Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: OMB + PAR/r + DAS + R 1-8	80	71
			Arm 2: PAR/r + DAS + R 1-12	41	35
			Arm 3: OMB + PAR/r + R 1-12	39*	33*
			Arm 4: OMB + PAR/r + R 1-12	40*	37*
			Arm 5: OMB + PAR/r + DAS 1-12	79	72
			Arm 6: OMB + PAR/r + DAS + R 1-12	39*	38*

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
			Arm 7: OMB + PAR/r + DAS + R 1-12	40*	38*
			Arm 8: OMB + PAR/r + DAS + R 1-24	40*	37*
			Arm 9: OMB + PAR/r + DAS + R 1-24	40*	36*
			Arm 10: OMB + PAR/r + R 1-12	45	40
			Arm 11: OMB + PAR/r + DAS + R 1-12	23*	21*
			Arm 12: OMB + PAR/r + DAS + R 1-12	22*	21*
			Arm 13: OMB + PAR/r + DAS + R 1-24	23*	21*
			Arm 14: OMB + PAR/r + DAS + R 1-24	20*	20*
Foster et al., 2015, BOSON, 2013-002641-11	Open label, Randomized, Multicentre	Genotype: 2 or 3 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SOF + R 1-16	91	70
			Arm 2: SOF + R 1-24	94	83
			Arm 3: SOF + PR 1-12	94	89
Merck & Co, 2015, 2015, C-EDGE CO-INFECTION, NCT02105662	Open label, Non-randomized	Genotype: 1, 4, 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HIV co-infected	Arm 1: GZR + EBR 1-12	218	207
Merck & Co, 2015, C-EDGE CO-STAR, NCT02105688	Double blind, Randomized, Multicentre	Genotype: 1, 4, 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: On opiate substitution therapy (OST) for at least 3 months	Arm 1: GZR + EBR 1-12	198	189
			Arm 2: Placebo 1-12, Unblinding 13-16, GZR + EBR 17-28		
Merck & Co, 2015, C-EDGE	Open label, Randomized,	Genotype: 1, 4, 6 Treatment history:	Arm 1: GZR + EBR 1-12	105	97
			Arm 2: GZR + EBR + R 1-12	104	98

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
TE, NCT02105701	Multicentre	Experienced Fibrosis status: Mixed Other characteristics:	Arm 3: GZR + EBR 1-16	105	97
			Arm 4: GZR + EBR + R 1-16	106	103
Merck & Co, 2015, C-EDGE TN, NCT02105467[1,2]	Double blind, Randomized, Multicentre	Genotype: 1, 4, 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: GZR + EBR 1-12	316	299
			Arm 2: Placebo 1-12, 13-16 Unblinding, GZR + EBR 17-28		
Charlton et al., 2015, NCT01687270	Open label, Non-randomized, Multicentre	Genotype: Any Treatment history: Mixed Fibrosis status: Mixed Other characteristics: Post-transplant, HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: SOF + R 1-24	40	28
Chayama et al., 2015, NCT01672983	Open label, Randomized, Multicentre	Genotype: 1b or 2 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: HCV RNA level greater than 10,000 IU/mL, no HIV	Arm 1: OMB + PAR/r 1-12	18*	18*
			Arm 2: OMB + PAR/r 1-12	18*	16*
			Arm 3: OMB + PAR/r 1-24	19*	19*
			Arm 4: OMB + PAR/r 1-24	18*	18*
Chulanov et al., 2014, NCT01896193	Open label, Randomized, Multicentre	Genotype: 1 or 3 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1a: SOF + R 1-16	32	16
			Arm 1b: SOF + R 1-16	30	26
			Arm 2a: SOF + R 1-24	34	26
			Arm 2b: SOF + R 1-24	31	28
Hézode et al., 2014, COMMAND-1, AI444010	Double blind, Randomized	Genotype: 1 or 4 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HCV	Arm 1: DCV + PR 1-12, DCV + PR 13-24 or PR 13-24 or PR 13-48	159	103
			Arm 2: DCV + PR 1-12, DCV + PR 13-24 or PR 13-24 or PR 13-48	158	106

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
		RNA >100,000 IU/ml	Arm 3: PR 1-48	78	29
Hézode et al., 2014, COMMAND-4, AI444042	Double blind, Randomized	Genotype: 4 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HCV RNA >10,000 IU/ml	Arm 1: DCV + PR 1-24 or DCV + PR 1-24, PR 25-48	82	60
			Arm 2: PR 1-48	42	18
Hayashi et al., 2014, CONCERTO-1, NCT01292239	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	123	109
			Arm 2: PR 1-48	60	37
Izumi et al., 2014, CONCERTO-2, NCT01288209	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	53	28
			Arm 2: SMV + PR 1-24 or SMV + PR 1-24, PR 25-48	53	19
Izumi et al., 2014, CONCERTO-3, NCT01290731	Open label, Non-randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	49	47

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Kwo et al., 2014, CORAL-1, NCT01782495	Open label, Non-randomized, Multicentre	Genotype: 1 or 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: On immunosuppressant regimen based on either tacrolimus or cyclosporine, pre- or post- liver or renal transplant	Arm 1: OMB + PAR/r + DAS + R 1-24	34	33
Merck & Co, 2015, C-SALVAGE, NCT02105454	Open label, Non-randomized, Multicentre	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: GZR + EBR + R 1-12	79	76
C-SALT, NCT02115321	Open label, Non-randomized, Multicentre	Genotype: 1, 4, or 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: Child-Pugh scale from 7 to 9 and not anticipated to receive a liver transplant within the next 36 weeks	Arm 1: GZR + EBR 1-12	30	27
			Arm 2: GZR + EBR 1-12	10	10
			Arm 3: GZR + EBR 1-12 (ongoing)		
			Arm 4: GZR + EBR 1-12 (ongoing)		
Merck & Co, 2015, C-SCAPE, NCT01932762	Open label, Non-randomized, Multicentre	Genotype: 2, 4, 5, 6 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: GZR + EBR + R 1-12	18	17
			Arm 2: GZR + EBR 1-12	18	13

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Merck & Co, 2015, C-SURFER, NCT02092350	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: Chronic kidney disease (defined as glomerular filtration rate ≤ 29), no HIV	Arms 1 & 2: GZR + EBR 1-12	122	115
			Arm 3: Placebo 1-12, 13-16 Unblinding, GZR + EBR 17-28		
Merck & Co, 2015, C-SWIFT, NCT02133131	Open label, Randomized, Single-centre	Genotype: 1 or 3 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: GZR + EBR + SOF 1-4	31	10
			Arm 2: GZR + EBR + SOF 1-6	30	26
			Arm 3: GZR + EBR + SOF 1-6	20	16
			Arm 4: GZR + EBR + SOF 1-8	21	17
			Arm 5: GZR + EBR + SOF 1-8	15	14
			Arm 6: GZR + EBR + SOF 1-12	14	14
			Arm 7: GZR + EBR + SOF 1-12	12	10
Merck & Co, 2015, C-WORTHY, NCT01717326	Open label, Randomized, Multicentre	Genotype: 1 or 3 Treatment history: Mixed Fibrosis status: Mixed Other characteristics:	Arm 1: GZR + EBR + R 1-12	25	25
			Arm 2: GZR + EBR + R 1-12	27	24
			Arm 3: GZR + EBR 1-12	13	13
			Arm 4: GZR + EBR + R 1-8	30	24
			Arm 5: GZR + EBR + R 1-12	33	30
			Arm 6: GZR + EBR 1-12	31	30
			Arm 7: GZR + EBR + R 1-12	31	28
			Arm 8: GZR + EBR 1-12	29	28
			Arm 9: GZR + EBR + R 1-18	32	31
			Arm 10: GZR + EBR 1-18	31	29
			Arm 11: GZR + EBR + R 1-12	32	30

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
			Arm 12: GZR + EBR 1-12	33	30
			Arm 13: GZR + EBR + R 1-18	33	33
			Arm 14: GZR + EBR 1-18	32	31
			Arm 15: GZR + EBR + R 1-12	29	28
			Arm 16: GZR + EBR 1-12	30	26
			Arm 17: GZR + EBR + R 1-8	30	27
			Arm 18: GZR + EBR 1-8	31	29
			Arm 19: GZR + EBR + R 1-12	20	9
			Arm 20: GZR + EBR + R 1-18	21	12
Dieterich et al., 2014, NCT01479868	Open label, Non-randomized, Multicentre	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HIV co-infection, HCV RNA ≥ 10,000 IU/mL	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	106	78
			Arm 1a: SMV + PR 1-12, PR 13-24 or PR 13-48	53	42
			Arm 1b: SMV + PR 1-12, PR 13-24 or PR 13-48	15	13
			Arm 1c: SMV + PR 1-12, PR 13-24 or PR 13-48	10	7
			Arm 1d: SMV + PR 1-12, PR 13-24 or PR 13-48	28	16
Doss et al., 2015	Open label, Randomized, Multicentre	Genotype: 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ⩾10,000 IU/ml, BMI ≥ 18 kg/m2, no HIV	Arm 1: SOF + R 1-12 (naïve)	25	21
			Arm 1: SOF + R 1-12 (experienced)	27	19
			Arm 2: SOF + R 1-24 (naïve)	24	22
			Arm 2: SOF + R 1-24 (experienced)	27	24
Hayashi et al., 2014, DRAGON, NCT00996476	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	27*	21*
			Arm 2: SMV + PR 1-24 or SMV + PR 1-24, PR 25-48	13*	10*
			Arm 3: SMV + PR 1-12, PR 13-24 or PR 13-48	26*	20*
			Arm 4: SMV + PR 1-24 or SMV + PR 1-24, PR 25-48	13*	12*

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
		RNA ⩾100,000 IU/ml	Arm 5: PR 1-48	13*	6*
Gane et al., 2013, ELECTRON, NCT01260350	Open label, Randomized, Multicentre	Genotype: 1, 2, 3 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 50,000 IU/mL, no HIV	Arm 1: SOF + R 1-12	10	10
			Arm 2: SOF + PR 1-4, SOF + R 5-12	9	9
			Arm 3: SOF + PR 1-8, SOF + R 9-12	10	10
			Arm 4: SOF + PR 1-12	11	11
			Arm 5: SOF 1-12	10	6
			Arm 6: SOF + PR 1-8	10	10
			Arm 7: SOF + R 1-12	10	1
			Arm 8: SOF + R 1-12	25	21
Gane et al., 2014, ELECTRON, NCT01260350			Arm 9: SOF + LDV + R 1-12	25	25
			Arm 10: SOF + LDV + R 1-6	25	17
			Arm 11: SOF + LDV + R 1-12	9	9
			Arm 12: SOF + LDV 1-12	10	7
			Arm 13: SOF + LDV + R 1-12	9	9
Gane et al., 2015, ELECTRON-2, NCT01826981	Open label, Randomized, Multicentre	Genotype: 1, 2, 3, 6 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 10,000 IU/mL	Arm 1: SOF + LDV 1-12	25	16
			Arm 2: SOF + LDV + R 1-12	26	26
			Arm 3: SOF + LDV + R 1-12	50	41
			Arm 4: SOF + LDV 1-12	25	24
Osinusi et al., 2015, ERADICATE, NCT01878799	Open label, Non-randomized, Single-centre	Genotype: 1a, 1b, or mixed 1a/1b Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HIV co-infected	Arm 1: SOF + LDV 1-12	13	13
			Arm 2: SOF + LDV 1-12	37	36

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Lawitz et al., 2013, FISSION, NCT01497366	Open label, Randomized, Multicentre	Genotype: 2 or 3 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SOF + R 1-12	253	170
			Arm 2: PR 1-24	243	162
Lawitz et al., 2013, NEUTRINO, NCT01641640	Open label, Non-randomized, Multicentre	Genotype: 1, 4, 5, 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics:	Arm 1: SOF + PR 1-12	327	296
Flamm et al., 2013, P05685AM2, NCT00845065	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: PR 1-48	67*	14*
			Arm 2: PR 1-4, BOC + PR 5-48	134*	86*
Gane et al., 2014, NCT01958281 Martin et al., 2015, NCT01958281	Open label, Non-randomized, Multicentre	Genotype: 1, 3, 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: SOF + R 1-24	10	4
			Arm 2: SOF + R 1-24	10	6
Kumada et al., 2015, GIFT-I, NCT02023099	Double blind, Randomized, Multicentre	Genotype: 1b Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: OMB + PAR/r 1-12	215	204
			Arm 2: Placebo 1-12, OMB + PAR/r 13-24	106	104
			Arm 3: OMB + PAR/r 1-12	42	38

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Hayashi et al., 2012, NCT00780910	Open label, Non-randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: TVR + PR 1-12, PR 13-24	109*	96*
Hayashi et al., 2012, NCT00781274	Open label, Non-randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: TVR + PR 1-12, PR 13-24	32*	11*
Hezode et al., 2015, HEPCAT, NCT01125189	Double blind, Randomized, Multicentre	Genotype: 1 or 4 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HCV RNA viral load of ≥100,000 IU/mL, BMI between 18 and 35, no HIV	Arm 1 (genotype 1): DCV + PR 1-12, DCV + PR 13-24 or PR 13-24 or PR 13-48	147	95
			Arm 1 (genotype 4): DCV + PR 1-12, DCV + PR 13-24 or PR 13-24 or PR 13-48	12	9
			Arm 2 (genotype 1): DCV + PR 1-12, DCV + PR 13-24 or PR 13-24 or PR 13-48	146	88
			Arm 2 (genotype 4): DCV + PR 1-12, DCV + PR 13-24 or PR 13-24 or PR 13-48	12	12
			Arm 3 (genotype 1): PR 1-48	72	26
			Arm 3 (genotype 4): PR 1-48	6	3
Mandorfer et al., 2015, HIVCOBOC-RGT, NCT01925183	Open label, Non-randomized, Single-centre	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HIV co-infection	Arm 1: PR 1-4, BOC + PR 5-28	12	12
			Arm 2: PR 1-4, BOC + PR 5-48	6	3

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Sherman et al., 2011, ILLUMINATE, NCT00758043	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics:	Arm 1: TVR + PR 1-12, PR 13-24	162*	149*
			Arm 2: TVR + PR 1-12, PR 13-48	160*	140*
			Arm 3: TVR + PR 1-12, PR 13-48	118*	76*
Afdhal et al., 2014, ION-1, NCT01701401	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: SOF + LDV 1-12	214	211
			Arm 2: SOF + LDV + R 1-12	217	211
			Arm 3: SOF + LDV 1-24	217	212
			Arm 4: SOF + LDV + R 1-24	217	215
Afdhal et al., 2014, ION-2, NCT01768286	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: SOF + LDV 1-12	109	102
			Arm 2: SOF + LDV + R 1-12	111	107
			Arm 3: SOF + LDV 1-24	109	108
			Arm 4: SOF + LDV + R 1-24	111	110
Kowdley et al., 2014, ION-3, NCT01851330	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: SOF + LDV 1-8	215	202
			Arm 2: SOF + LDV + R 1-8	216	201
			Arm 3: SOF + LDV 1-12	216	206
Naggie et al., 2015, ION-4, NCT02073656	Open label, Non-randomized, Multicentre	Genotype: 1 or 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HIV co-infected, HCV RNA ≥ 10,000 IU/mL	Arm 1: SOF + LDV 1-12	335	322

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Kawakami et al., 2014, UMIN 000006758	Open label, Randomized, Multicentre	Genotype: 1b Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥100,000 IU/ml, no HIV	Arm 1: TVR + PR 1-12, PR 13-24	26	24
			Arm 2: TVR + PR 1-12, PR 13-24	26	24
Kumada et al., 2012[3]	Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HCV RNA levels ≥ 100,000 IU/mL	Arm 1: TVR + PR 1-12, PR 13-24	126*	92*
			Arm 2: PR 1-48	63*	31*
Lai et al., 2016, NCT02021643	Open label, Randomized	Genotype: 1, 2, 3, 6 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: SOF + R 1-12	10	10
			Arm 2: SOF + R 1-16	11	11
			Arm 3: SOF + R 1-24	10	9
Lawitz et al., 2015	Open label, Non-randomized, Single-centre	Genotype: 2 or 3 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: No HIV, HCV RNA ≥10,000 IU/mL, BMI ≥ 18 kg/m2	Arm 1: SOF + PR 1-12	24	20

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Lim at al., 2015, NCT02021656	Open label, Non-randomized, Multicentre	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: SOF + LDV 1-12	178	175
Lawitz et al., 2014, LONESTAR, NCT01726517	Open label, Randomized, Single-centre	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 10,000 IU/mL	Arm 1: SOF + LDV 1-8	20	19
			Arm 2: SOF + LDV + R 1-8	21	21
			Arm 3: SOF + LDV 1-12	19	18
			Arm 4: SOF + LDV 1-12	19	18
			Arm 5: SOF + LDV + R 1-12	21	21
Dore et al., 2016, MALACHITE-I, NCT01854697	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: OMB + PAR/r + DAS + R 1-12	69	67
			Arm 2: TVR + PR 1-12, PR 13-24 or PR 13-48	34	28
			Arm 3: OMB + PAR/r + DAS + R 1-12	84	83
			Arm 4: OMB + PAR/r + DAS 1-12	83	81
			Arm 5: TVR + PR 1-12, PR 13-24 or PR 13-48	41	32
Dore et al., 2016, MALACHITE-II, NCT01854528	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: OMB + PAR/r + DAS + R 1-12	101	100
			Arm 2: TVR + PR 1-12, PR 13-24 or PR 13-48	47	31
Marcellin et al., 2011, NCT00528528	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: No	Arm 1: TVR + PR 1-12, PR 13-24 or PR 13-48	40*	34*
			Arm 2: TVR + PR 1-12, PR 13-24 or PR 13-48	42*	34*
			Arm 3: TVR + PR 1-12, PR 13-24 or PR 13-48	40*	33*

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
		cirrhosis Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 4: TVR + PR 1-12, PR 13-24 or PR 13-48	39*	32*
Bernabucci et al., 2014, MEN_BOC, NCT01457937	Open label, Randomized, Single-centre	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: No HIV, Menopausal females	Arm 1: PR 1-4, BOC + PR 5-48 or PR 1-4, BOC + PR 5-36 or BOC + PR 5-36, PR 37-48	56*	25*
Mizokami et al., 2015, NCT01975675	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: No HIV, HCV RNA ≥ 100,000 IU/mL	Arm 1: SOF + LDV 1-12	171	171
			Arm 2: SOF + LDV + R 1-12	170	167
Lawitz et al., 2015, NAVIGATOR, NCT01458535	Open label, Non-randomized, Multicentre	Genotype: 1, 2, 3 Treatment history: Naïve Fibrosis status: Mixed Other characteristics:	Arm 1a: OMB + PAR/r + R 1-12	10	10
			Arm 1b: OMB + PAR/r + R 1-12	10	5
			Arm 2a: OMB + PAR/r 1-12	10	6
			Arm 2b: OMB + PAR/r 1-12	11	1
Ogawa et al., 2013, UMIN 000011105	Open label, Non-randomized, Multicentre	Genotype: 1b Treatment history: Experienced Fibrosis status: F3-F4 Other characteristics: No HIV	Arm 1: TVR + PR 1-12, PR 13-24	102*	71*
Buti et al., 2014,	Open label,	Genotype: 1	Arm 1: TVR + PR 1-12, PR 13-24 or PR 13-48	369	274

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
OPTIMIZE, NCT01241760	Randomized, Multicentre	Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HCV RNA > 1,000 IU/mL, no HIV	Arm 2: TVR + PR 1-12, PR 13-24 or PR 13-48	371	270
Oze et al., 2015, UMIN 000007313; UMIN 000007330	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA > 100,000 IU/ml, no HIV	Arm 1: TVR + PR 1-12, PR 13-24	41*	35*
			Arm 2: TVR + PR 1-12, PR 13-24	40*	34*
Sulkowski et al., 2013, P05411 AM4, NCT00959699	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve (except for non-toxic herbal remedies) Fibrosis status: Mixed Other characteristics: HIV-1 co-infected, HIV-1 RNA <50 copies/mL, no HIV-2	Arm 1: PR 1-48	34	9
			Arm 2: PR 1-4, BOC + PR 5-48	64	40
Hezode et al., 2015, PEARL-1, NCT01685203	Open label, Randomized, Multicentre	Genotype: 1b or 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA level > 10,000 IU/mL, No HIV, BMI ≥ 18 and < 38 kg/m2	Arm 1: OMB + PAR/r 1-12	44	40
			Arm 2: OMB + PAR/r + R 1-12	42	42
			Arm 3: OMB + PAR/r + R 1-12	49	49
Lawitz et al., 2015, PEARL-1, NCT01685203			Arm 4: OMB + PAR/r 1-12	42	40
			Arm 5: OMB + PAR/r 1-12	40	36
			Arm 6: OMB + PAR/r 1-24	47	46
			Arm 7: OMB + PAR/r 1-24	52	50
Andreone et al.,	Open label,	Genotype: 1b	Arm 1: OMB + PAR/r + DAS + R 1-12	88	85

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
2014, PEARL-2, NCT01674725	Randomized, Multicentre	Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 2: OMB + PAR/r + DAS 1-12	91	91
Ferenci et al., 2014, PEARL-3, NCT01767116	Double blind, Randomized, Multicentre	Genotype: 1b Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: OMB + PAR/r + DAS + R 1-12	210	209
			Arm 2: OMB + PAR/r + DAS 1-12	209	207
Ferenci et al., 2014, PEARL-4, NCT01833533	Double blind, Randomized, Multicentre	Genotype: 1a Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: OMB + PAR/r + DAS + R 1-12	100	97
			Arm 2: OMB + PAR/r + DAS 1-12	205	185
Pearlman et al., 2015, NCT02168361	Open label, Randomized, Single-centre	Genotype: 1a Treatment history: Mixed Fibrosis status: Cirrhosis Other characteristics: No HIV	Arm 1: SMV + SOF 1-12	58	54
			Arm 2: SOF + PR 1-12	24	18
Sulkowski et al., 2014, PHOTON-	Open label, Non-	Genotype: 1, 2, 3 Treatment history: Mixed	Arm 1: SOF + R 1-24	114	87
			Arm 2: SOF + R 1-12	68	51

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
1, NCT01667731	randomized, Multicentre	Fibrosis status: Mixed Other characteristics: HIV-1 co-infected, HCV RNA > 10,000 IU/mL	Arm 3: SOF + R 1-24	41	38
Molina et al., 2015, PHOTON-2, NCT01783678	Open label, Non-randomized, Multicentre	Genotype: 1, 2, 3, 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HIV-1 co-infected, HCV RNA > 10,000 IU/mL	Arm 1: SOF + R 1-24	112	95
			Arm 2: SOF + R 1-24	57	52
			Arm 3: SOF + R 1-24	49	42
			Arm 4: SOF + R 1-24	31	26
Fried et al., 2013, PILLAR, NCT00882908	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV RNA > 100,000 IU/mL, no HIV	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	78	65
			Arm 2: SMV + PR 1-24 or SMV + PR 1-24, PR 25-48	75	57
			Arm 3: SMV + PR 1-12, PR 13-24 or PR 13-48	77	62
			Arm 4: SMV + PR 1-24 or SMV + PR 1-24, PR 25-48	79	68
			Arm 5: PR 1-48	77	51
Pol et al., 2015	Open label, Non-randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics:	Arm 1: SOF + PR 1-12	80	63
Merck & Co, 2016, PN077, NCT02358044	Open label, Randomized, Multicentre	Genotype: 1, 4, 6 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: GZR + EBR 1-12	129	128
			Arm 2: SOF + PR 1-12	126	114

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Jacobson et al., 2013, POSITRON, NCT01542788	Double blind, Randomized, Multicentre	Genotype: 2 or 3 Treatment history: Mixed Fibrosis status: Mixed Other characteristics:	Arm 1: Placebo	68	0
			Arm 2: SOF + R 1-12	207	161
Jacobson et al., 2013, FUSION, NCT01604850	Double blind, Randomized, Multicentre	Genotype: 2 or 3 Treatment history: Experienced Fibrosis status: Mixed Other characteristics:	Arm 1: SOF + R 1-12	100	50
			Arm 2: SOF + R 1-16	95	69
Forns et al., 2014, PROMISE, NCT01281839	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	260	206
			Arm 2: PR 1-48	133	48
Lawitz et al., 2013, PROTON, NCT01188772	Double blind, Randomized, Multicentre	Genotype: 1, 2, 3 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: BMI > 18 kg/m2 and < 36 kg/m2, no HIV	Arm 1: SOF + PR 1-12, PR 13-24 or PR 13-48	48	43
			Arm 2: SOF + PR 1-12, PR 13-24 or PR 13-48	47	43
			Arm 3: PR 1-48	26	15
			Arm 4: SOF + PR 1-12	25	23
McHutchison et al., 2009, PROVE1, NCT00336479	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: Detectable plasma HCV RNA, no HIV	Arm 1: TVR + PR 1-12, PR 13-24	79*	48*
			Arm 2: TVR + PR 1-12, PR 13-48	79*	53*
			Arm 3: TVR + PR 1-12	17*	6*
			Arm 4: PR 1-48	75*	31*

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Hezode et al., 2009, PROVE2, NCT00372385	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: Detectable plasma HCV RNA, no HIV	Arm 1: TVR + PR 1-12, PR 13-24	81*	56*
			Arm 2: TVR + PR 1-12	82*	49*
			Arm 3: TVR + P 1-12	78*	28*
			Arm 4: PR 1-36	82*	38*
McHutchison et al., 2010, PROVE3, NCT00420784	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 10,000 IU/mL	Arm 1: TVR + PR 1-12, PR 13-24	115*	59*
			Arm 2: TVR + PR 1-24, PR 25-48	113*	60*
			Arm 3: TVR + P 1-24	111*	27*
			Arm 4: PR 1-48	114*	16*
Vierling et al., 2014, PROVIDE, NCT00910624	Open label, Non-randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics:	Arm 1a: PR 1-4, BOC + PR 5-44 or BOC + PR 1-44	52*	20*
			Arm 1b: PR 1-4, BOC + PR 5-44 or BOC + PR 1-44	85*	57*
			Arm 1c: PR 1-4, BOC + PR 5-44 or BOC + PR 1-44	29*	27*
Jacobson et al., 2014, QUEST-1, NCT01289782	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	264	210
			Arm 2: PR 1-48	130	65
Manns et al., 2014, QUEST-2, NCT01290679	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	257	209
			Arm 2: PR 1-48	134	67

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Zeuzem et al., 2011, REALIZE, NCT00703118	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 1000 IU/mL	Arm 1: TVR + PR 1-12, PR 13-48	266*	171*
			Arm 2: PR 1-4, TVR + PR 5-16, PR 17-48	264*	175*
			Arm 3: PR 1-48	132*	22*
Foster et al., 2013, REALIZE, NCT00703118			Arm 2a: PR 1-4, TVR + PR 5-16, PR 17-48	126*	114*
			Arm 2b: PR 1-4, TVR + PR 5-16, PR 17-48	45*	26*
			Arm 2c: PR 1-4, TVR + PR 5-16, PR 17-48	69*	21*
Bacon et al., 2011, RESPOND-2, NCT00708500	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: PR 1-48	80*	17*
			Arm 2: PR 1-4, BOC + PR 5-36 or BOC + PR 5-36, PR 37-48	162*	95*
			Arm 3: PR 1-4, BOC + PR 5-48	161*	107*
Moreno et al., 2015, RESTORE, NCT01567735	Open label, Non-randomized, Multicentre	Genotype: 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA >10,000 IU/mL, no HIV	Arm 1a: SMV + PR 1-12, PR 13-24 or PR 13-48	35	29
			Arm 1b: SMV + PR 1-12, PR 13-24 or PR 13-48	22	19
			Arm 1c: SMV + PR 1-12, PR 13-24 or PR 13-48	10	6
			Arm 1d: SMV + PR 1-12, PR 13-24 or PR 13-48	40	16
Rodriguez-Torres et al., 2015, NCT01565889	Open label, Non-randomized, Single-centre	Genotype: Any Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HIV-1 co-infected	Arm 1: SOF + PR 1-12	23	21

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Ruane et al., 2015, NCT01713283	Open label, Randomized, Single-centre	Genotype: 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SOF + R 1-12	31	21
			Arm 2: SOF + R 1-24	29	27
Feld et al., 2014, SAPPHIRE-1, NCT01716585	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: OMB + PAR/r + DAS + R 1-12	473	455
			Arm 2: Placebo 1-12, OMB + PAR/r + DAS + R 13-24		
Zeuzem et al., 2014, SAPPHIRE-2, NCT01715415	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: OMB + PAR/r + DAS + R 1-12	297	286
			Arm 2: Placebo 1-12, OMB + PAR/r + DAS + R 13-24		
Bourliere et al., 2015, SIRIUS, NCT01965535	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Cirrhosis Other characteristics: HCV RNA ≥ 10,000 IU/mL	Arm 1: SOF + LDV + R 1-12	77	74
			Arm 2: SOF + LDV 1-24	77	75

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Charlton et al., 2015, SOLAR-1, NCT01938430	Open label, Non-randomized, Multicentre	Genotype: 1 or 4 Treatment history: Experienced (?) Fibrosis status: Mixed Other characteristics: Decompensated cirrhosis or post-transplant, no HIV	Arm 1: SOF + LDV 1-12	30	26
			Arm 2: SOF + LDV 1-24	27	24
			Arm 3: SOF + LDV 1-12	22	19
			Arm 4: SOF + LDV 1-24	23	20
			Arm 5: SOF + LDV 1-12	55	53
			Arm 6: SOF + LDV 1-24	56	55
			Arm 7: SOF + LDV 1-12	26	25
			Arm 8: SOF + LDV 1-24	25	24
			Arm 9: SOF + LDV 1-12	26	22
			Arm 10: SOF + LDV 1-24	26	23
			Arm 11: SOF + LDV 1-12	5	3
			Arm 12: SOF + LDV 1-24	4	3
			Arm 13: SOF + LDV 1-12	4	4
			Arm 14: SOF + LDV 1-24	2	2
Osinusi et al., 2013, SPARE, NCT01441180	Open label, Randomized, Single-centre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 2,000 IU/mL, BMI ≥ 18 kg/m2, no HIV	Arm 1: SOF + R 1-24	10	9
			Arm 2: SOF + R 1-24	25	17
			Arm 3: SOF + R 1-24	25	12

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Kwo et al., 2010, SPRINT-1, NCT00423670	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: PR 1-48	104*	39*
			Arm 2: PR 1-4, BOC + PR 5-28	103*	58*
			Arm 3: PR 1-4, BOC + PR 5-48	103*	77*
			Arm 4: BOC + PR 1-28	107*	58*
			Arm 5: BOC + PR 1-48	103*	69*
			Arm 6: BOC + PR 1-48	16*	8*
			Arm 7: BOC + PR 1-48	59*	21*
Poordad et al., 2011, SPRINT-2, NCT00705432	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: PR 1-48	363*	137*
			Arm 2: PR 1-4, BOC + PR 5-28 or BOC + PR 5-28, PR 29-48	368*	233*
			Arm 3: PR 1-4, BOC + PR 5-48	366*	242*
Kohli et al., 2015a, SYNERGY, NCT01805882	Open label, Non-randomized, Multicentre	Genotype: 1 or 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 2,000 IU/mL	Arm 1: SOF + LDV 1-12	20	20
Kohli et al., 2015b, SYNERGY, NCT01805882			Arm 2: SOF + LDV 1-12	21	20
Osinusi et al., 2014, SYNERGY, NCT01805882			Arm 3: SOF + LDV 1-12	14	14
Wilson et al., 2016, SYNERGY, NCT01805882			Arm 4: SOF + LDV 1-12	34	31

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Cotte et al., 2014, TelapreVIH, NCT01332955	Open label, Non-randomized, Single-centre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: HIV-1 co-infected, no HIV-2, HIV RNA <50 copies/mL	Arm 1: PR 1-4, TVR + PR 5-16, PR 17-48 or PR 17-72	69*	55*
Reau et al., 2015, TOPAZ-II, NCT02167945	Open label, Non-randomized, Multicentre	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA level greater than 1,000 IU/mL, no HIV	Arm 1: OMB + PAR/r + DAS ± R 1-12/1-24	615	586
Sulkowski et al., 2015, TURQUOISE-I, NCT01939197	Open label, Randomized, Multicentre	Genotype: 1 or 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HIV-1 co-infection, no HIV-2, HCV RNA > 1,000 IU/mL, HIV-1 RNA <40 copies/mL	Arm 1: OMB + PAR/r + DAS + R 1-12	31	29
			Arm 2: OMB + PAR/r + DAS + R 1-24	32	29
Poordad et al., 2014, TURQUOISE-II, NCT01704755	Open label, Randomized, Multicentre	Genotype: 1 Treatment history: Mixed Fibrosis status: Cirrhosis Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: OMB + PAR/r + DAS + R 1-12	208	191
			Arm 2: OMB + PAR/r + DAS + R 1-24	172	165

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Feld et al., 2016, TURQUOISE-III, NCT02219503	Open label, Non-randomized, Multicentre	Genotype: 1b Treatment history: Mixed Fibrosis status: Cirrhosis Other characteristics: HCV RNA > 1,000 IU/mL, no HIV	Arm 1: OMB + PAR/r + DAS 1-12	60	60
Zeuzem et al., 2014, VALENCE, NCT01682720	Double blind, Randomized, Multicentre	Genotype: 2 or 3 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: SOF + R 1-12	11	3
			Arm 2: SOF + R 1-24	250	213
Sulkowski et al., 2013, VX08-950-110, NCT00983853	Double blind, Randomized, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HIV-1 co-infected	Arm 1: TVR + PR 1-12, PR 13-48	7	5
			Arm 2: PR 1-48	6	2
			Arm 3: TVR + PR 1-12, PR 13-48	16	11
			Arm 4: PR 1-48	8	4
			Arm 5: TVR + PR 1-12, PR 13-48	15	12
			Arm 6: PR 1-48	8	4
Walsh et al., 2015, NCT02120300	Open label, Non-randomized, Multicentre	Genotype: 1, 2, 3, 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: Hemophilia A, B or C, Von Willebrand's disease, or HIV-1 co-infected, HCV RNA ≥ 1000 IU/mL	Arm 1: SOF + LDV 1-12	99	98
			Arm 2: SOF + LDV 1-24		
			Arm 3: SOF + R 1-12		

Citation(s), trial name, registration number	Study design	Populations description	Treatment arms	Arm (N)	SVR12 (n)
Wyles et al., 2015, NCT01987453	Open label, Non-randomized, Multicentre	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SOF + LDV + R 1-12	51	50

A6. **Priority question**: Please provide the adverse event rates for overall adverse events, discontinuation due to adverse events, anaemia, nausea, neutropenia, pruritus, and rash. For each of these, provide the number of events and number of patients in each arm for all treatment arms for all included RCTs.

Please see the table below.

Table 1: Rates of adverse events in trials identified from the systematic literature review

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
Jacobson et al., 2011, ADVANCE, NCT00627926	Arm 1: TVR + PR 1-12, PR 13-24 or PR 13-48	363	361	36	135	156	51	181	133
	Arm 2: TVR + PR 1-8, PR 9-24 or PR 9-48	364	362	37	141	146	62	165	129
	Arm 3: PR 1-48	361	354	26	70	112	68	131	88
Sulkowski et al., 2014, A1444040, NCT01359644	Arms 1 & 4: SOF 1, DCV + SOF 2-24	31	25	0	0	5		1	3
	Arms 2 & 5: DCV + SOF 1-24	28	26	1	0	9		1	0
	Arms 3 & 6: DCV + SOF + R 1-24	29	26	1	3	9		2	2
	Arm 7: DCV + SOF 1-12	41	38	0	0	8		1	2

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
	Arm 8: DCV + SOF + R 1-12	41	38	0	7	8		5	2
	Arm 9: DCV + SOF 1-24	21	16	0	0	0		1	0
	Arm 10: DCV + SOF + R 1-24	20	20	0	3	2		2	2
Poordad et al., 2015, ALLY-1, NCT02032875	Arm 1: DCV + SOF + R 1-12	60		1	12	10			
	Arm 2: DCV + SOF + R 1-12	53		1	10	3			
Wyles et al., 2015, ALLY-2, NCT02032888	Arm 1: DCV + SOF 1-12	101	74	0	0	14		2	6
	Arm 2: DCV + SOF 1-8	50	29	0	0	4		1	0
	Arm 3: DCV + SOF 1-12	52	37	0	1	8		1	3
Nelson et al., 2015, ALLY-3, NCT02032901	Arms 1 & 2: DCV + SOF 1-12	152		0		18			
Fontaine et al., 2015, ANRS HC29 BOCEPRETRANS PLANT, NCT01463956	Arm 1: PR 1-4, BOC + PR 5-48	51		20	5		13		
Zeuzem et al., 2014, ASPIRE, NCT00980330	Arm 1: SMV + PR 1-12, PR 13-48	66		6	15	17	16	19	13
	Arm 2: SMV + PR 1-24, PR 25-48	65		3	11	10	15	26	14
	Arm 3: SMV + PR 1-48	66		2	12	20	15	21	18
	Arm 4: SMV + PR 1-12, PR 13-48	66		3	10	20	18	20	17
	Arm 5: SMV + PR 1-24, PR 25-48	68		2	16	11	18	25	18
	Arm 6: SMV + PR 1-48	65		5	13	17	20	24	25
	Arm 7: PR 1-48	66		3	13	14	11	11	12

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
Foster et al., 2015, ASTRAL-3, NCT02201953	Arm 2: SOF + R 1-24	275	260	9		58		35	
Kowdley et al., 2013, ATOMIC, NCT01329978	Arm 1: SOF + PR 1-12	52	51	3	7	16	12		7
	Arm 2: SOF + PR 1-24	125	121	18	31	43	25		26
	Arm 3: SOF + PR 1-12, SOF 13-24 or SOF + R 13-24	155	153	3	34	48	22		38
Reddy et al., 2015, ATTAIN, NCT01485991	Arm 1: SMV + PR 1-12, PR 13-48	379	347	0	51	64	69	122	81
	Arm 2: TVR + PR 1-12, PR 13-48	384	371	4	144	109	52	170	119
Kowdley et al., 2014, AVIATOR, NCT01464827	Arm 1: OMB + PAR/r + DAS + R 1-8	80		1	5	12		12	10
	Arm 2: PAR/r + DAS + R 1-12	41		0	1	7		3	2
	Arm 3: OMB + PAR/r + R 1-12	39		0	2	7		3	3
	Arm 4: OMB + PAR/r + R 1-12	40		0	1	9		5	3
	Arm 5: OMB + PAR/r + DAS 1-12	79		0	1	11		3	6
	Arm 6: OMB + PAR/r + DAS + R 1-12	39			3	8		2	5
	Arm 7: OMB + PAR/r + DAS + R 1-12	40			4	11		4	6
	Arm 8: OMB + PAR/r + DAS + R 1-24	40			4	11		6	8
	Arm 9: OMB + PAR/r + DAS + R 1-24	40			2	9		5	6
	Arm 10: OMB + PAR/r + R 1-12	45		1	3	6		6	2
	Arm 11: OMB + PAR/r + DAS + R 1-12	23		0	2	5		4	1
	Arm 12: OMB + PAR/r + DAS + R 1-12	22		0	1	4		3	3
	Arm 13: OMB + PAR/r + DAS + R 1-24	23			1	4		4	4
	Arm 14: OMB + PAR/r + DAS + R 1-24	20			1	4		2	2

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
Foster et al., 2015, BOSON, 2013-002641-11	Arm 1: SOF + R 1-16	196	185	3		32		21	24
	Arm 2: SOF + R 1-24	199	188	3		34		24	27
	Arm 3: SOF + PR 1-12	197	195	2		50		22	39
Merck & Co, 2015, 2015, C-EDGE CO-INFECTION, NCT02105662	Arm 1: GZR + EBR 1-12	218	161	0		20		5	4
Merck & Co, 2015, C-EDGE CO-STAR, NCT02105688	Arm 1: GZR + EBR 1-12	201	166	2		23			
	Arm 2: Placebo 1-12, Unblinding 13-16, GZR + EBR 17-28	100	83	2		9			
Merck & Co, 2015, C-EDGE TE, NCT02105701	Arm 1: GZR + EBR 1-12	105	74	1	0	9		1	
	Arm 2: GZR + EBR + R 1-12	104	85	1	12	15		11	
	Arm 3: GZR + EBR 1-16	105	77	0	0	4		5	
	Arm 4: GZR + EBR + R 1-16	106	95	5	17	18		11	
Merck & Co, 2015, C-EDGE TN, NCT02105467[1,2]	Arm 1: GZR + EBR 1-12	316	213	3	2	28	2	7	6
	Arm 2: Placebo 1-12, 13-16 Unblinding, GZR + EBR 17-28	105	72	1	0	8	0	8	1
Charlton et al., 2015, NCT01687270	Arm 1: SOF + R 1-24	40	39	2	8	8		3	
Chayama et al., 2015, NCT01672983	Arm 1: OMB + PAR/r 1-12	18	14	0					0
	Arm 2: OMB + PAR/r 1-12	18	15	1					0
	Arm 3: OMB + PAR/r 1-24	19	16	0					2
	Arm 4: OMB + PAR/r 1-24	18	15	0					3

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
Chulanov et al., 2014, NCT01896193	Arms 1a & 1b: SOF + R 1-16	62	28	0					
	Arms 2a & 2b: SOF + R 1-24	65	45	0					
Hézode et al., 2014, COMMAND-1, AI444010	Arm 1: DCV + PR 1-12, DCV + PR 13-24 or PR 13-24 or PR 13-48	159		7		35		35	34
	Arm 2: DCV + PR 1-12, DCV + PR 13-24 or PR 13-24 or PR 13-48	159		7		34		40	25
	Arm 3: PR 1-48	78		7		24		33	32
Hézode et al., 2014, COMMAND-4, AI444042	Arm 1: DCV + PR 1-24 or DCV + PR 1-24, PR 25-48	82		4	20		12	25	
	Arm 2: PR 1-48	42		3	12		11	13	
Hayashi et al., 2014, CONCERTO-1, NCT01292239	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	123		6	70	16	8	35	57
	Arm 2: PR 1-48	60		5	36	12	1	18	37
Izumi et al., 2014, CONCERTO-2, NCT01288209	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	53	53	2	28		28	16	20
	Arm 2: SMV + PR 1-24 or SMV + PR 1-24, PR 25-48	53	52	2	31		28	12	23
Izumi et al., 2014, CONCERTO-3, NCT01290731	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	49	49	2	22		30	19	16
Kwo et al., 2014, CORAL-1, NCT01782495	Arm 1: OMB + PAR/r + DAS + R 1-24	34	33	1	10	8			7
Merck & Co, 2015, C-SALVAGE, NCT02105454	Arm 1: GZR + EBR + R 1-12	79	63	1	6	9		3	3
C-SALT,	Arm 1: GZR + EBR 1-12	30	25	0		3			

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
NCT02115321	Arm 2: GZR + EBR 1-12	10	8	0		2			
	Arm 3: GZR + EBR 1-12								
	Arm 4: GZR + EBR 1-12								
Merck & Co, 2015, C-SCAPE, NCT01932762	Arm 1: GZR + EBR + R 1-12	19	18	0		2			
	Arm 2: GZR + EBR 1-12	19	15	1		1			
Merck & Co, 2015, C-SURFER, NCT02092350	Arm 1: GZR + EBR 1-12	11	9	0	0	1	0	0	0
	Arm 2: GZR + EBR 1-12	111	85	0	2	17	1	4	2
	Arm 3: Placebo 1-12, 13-16 Unblinding, GZR + EBR 17-28	113	99	5	2	18	0	11	3
Merck & Co, 2015, C-SWIFT, NCT02133131	Arm 1: GZR + EBR + SOF 1-4	31	5	0		0		0	
	Arm 2: GZR + EBR + SOF 1-6	30	7	0		0		0	
	Arm 3: GZR + EBR + SOF 1-6	20	7	0		0		0	
	Arm 4: GZR + EBR + SOF 1-8	21	4	1		1		0	
	Arm 5: GZR + EBR + SOF 1-8	15	4	0		0		0	
	Arm 6: GZR + EBR + SOF 1-12	14	3	0		1		1	
	Arm 7: GZR + EBR + SOF 1-12	12	3	0		1		0	
Merck & Co, 2015, C-WORTHY, NCT01717326	Arm 1: GZR + EBR + R 1-12	25	22	0	3	5		1	1
	Arm 2: GZR + EBR + R 1-12	28	24	0	2	7		2	5
	Arm 3: GZR + EBR 1-12	12	11	0	0	2		0	1
	Arm 4: GZR + EBR + R 1-8	30	27	0	1	8		6	0
	Arm 5: GZR + EBR + R 1-12	33	24	0	0	6		4	3
	Arm 6: GZR + EBR 1-12	31	27	0	0	5		0	1

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
	Arm 7: GZR + EBR + R 1-12	31	24	0	1	4		2	3
	Arm 8: GZR + EBR 1-12	29	19	0	0	0		1	0
	Arm 9: GZR + EBR + R 1-18	32	28	2	4	4		5	7
	Arm 10: GZR + EBR 1-18	31	26	0	0	3		2	0
	Arm 11: GZR + EBR + R 1-12	32	26	1	2	4		1	2
	Arm 12: GZR + EBR 1-12	33	26	0	0	2		2	1
	Arm 13: GZR + EBR + R 1-18	33	32	0	5	5		10	1
	Arm 14: GZR + EBR 1-18	32	26	0	0	1		1	0
	Arm 15: GZR + EBR + R 1-12	29	19	0	2			3	
	Arm 16: GZR + EBR 1-12	30	16	0	0			0	
	Arm 17: GZR + EBR + R 1-8	30	22	0	0	5		4	3
	Arm 18: GZR + EBR 1-8	31	17	0	0	3		0	1
	Arm 19: GZR + EBR + R 1-12	20	17	0	3	3		1	3
	Arm 20: GZR + EBR + R 1-18	21	19	1	0	5		3	2
Dieterich et al., 2014, NCT01479868	Arms 1a, 1b, 1c, & 1d: SMV + PR 1-12, PR 13-24 or PR 13-48	106	102	3	22	27	30	21	17
Doss et al., 2015	Arm 1: SOF + R 1-12	52	39	0	6			2	
	Arm 2: SOF + R 1-24	51	42	0	10			9	
Hayashi et al., 2014, DRAGON, NCT00996476	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	27		1	8		12	5	17
	Arm 2: SMV + PR 1-24 or SMV + PR 1-24, PR 25-48	13		3	5		10	0	8
	Arm 3: SMV + PR 1-12, PR 13-24 or PR 13-48	26		3	6		14	4	15
	Arm 4: SMV + PR 1-24 or SMV + PR 1-24, PR 25-48	13		1	5		12	6	8

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
	Arm 5: PR 1-48	13		2	5		9	0	6
Gane et al., 2013, ELECTRON, NCT01260350	Arm 1: SOF + R 1-12	10	10	0	1	0		1	3
	Arm 2: SOF + PR 1-4, SOF + R 5-12	9	9	0	4	3		3	3
	Arm 3: SOF + PR 1-8, SOF + R 9-12	10	10	0	2	4		3	3
	Arm 4: SOF + PR 1-12	11	11	0	3	2		2	3
	Arm 5: SOF 1-12	10	10	0	0	3		0	1
	Arm 6: SOF + PR 1-8	10	10	0	3	2		2	6
	Arm 7: SOF + R 1-12	10	10	0	3	2		2	3
	Arm 8: SOF + R 1-12	25	25	0	5	11		0	4
Gane et al., 2014, ELECTRON, NCT01260350	Arm 9: SOF + LDV + R 1-12	25	24	1	3	6			4
	Arm 10: SOF + LDV + R 1-6	25	22	0	0	5			3
	Arm 11: SOF + LDV + R 1-12	9	9	0	0	3			1
	Arm 12: SOF + LDV 1-12	10	7	0	0	0			0
	Arm 13: SOF + LDV + R 1-12	9	8	0	0	4			0
Gane et al., 2015, ELECTRON-2, NCT01826981	Arm 1: SOF + LDV 1-12	25	25	1		9			1
	Arm 2: SOF + LDV + R 1-12	26	23	0		4			1
	Arm 3: SOF + LDV + R 1-12	50	45	0		5			7
	Arm 4: SOF + LDV 1-12	25	21	0		0			2
Osinusi et al., 2015, ERADICATE, NCT01878799	Arm 1: SOF + LDV 1-12	13	13	0		1			
	Arm 2: SOF + LDV 1-12	37	37	0		2			
Lawitz et al., 2013,	Arm 1: SOF + R 1-12	256	220	3	20	46	0	19	23

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
FISSION, NCT01497366	Arm 2: PR 1-24	243	233	26	28	70	30	42	43
Lawitz et al., 2013, NEUTRINO, NCT01641640	Arm 1: SOF + PR 1-12	327	310	5	68	112	54	54	59
Flamm et al., 2013, P05685AM2, NCT00845065	Arm 1: PR 1-48	67	67	3	22	18	12	8	5
	Arm 2: PR 1-4, BOC + PR 5-48	134	134	23	67	51	42	18	30
Gane et al., 2014, NCT01958281	Arm 1: SOF + R 1-24	10	10	1	5			3	3
Martin et al., 2015, NCT01958281	Arm 2: SOF + R 1-24	10	9	2	4				
Kumada et al., 2015, GIFT-I, NCT02023099	Arm 1: OMB + PAR/r 1-12	215	148	2		9			
	Arm 2: Placebo 1-12	106	60	0		4			
	Arm 2: OMB + PAR/r 13-24	106	68	0		1			
	Arm 3: OMB + PAR/r 1-12	42	31	1		3			
Hayashi et al., 2012, NCT00780910	Arm 1: TVR + PR 1-12, PR 13-24	109	109	19	96	24		20	39
Hayashi et al., 2012, NCT00781274	Arm 1: TVR + PR 1-12, PR 13-24	32	32	4	32	4		2	16
Hezode et al., 2015, HEPCAT, NCT01125189	Arm 1: DCV + PR 1-12, DCV + PR 13-24 or PR 13-24 or PR 13-48	159	156	7	32	56	26	56	54
	Arm 2: DCV + PR 1-12, DCV + PR 13-24 or PR 13-24 or PR 13-48	158	155	7	21	53	17	63	40
	Arm 3: PR 1-48	78	76	8	9	20	9	26	25

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
Mandorfer et al., 2015, HIVCOBOC-RGT, NCT01925183	Arm 1: PR 1-4, BOC + PR 5-28	14	14						
	Arm 2: PR 1-4, BOC + PR 5-48	7	7						
Sherman et al., 2011, ILLUMINATE, NCT00758043	Arm 1: TVR + PR 1-12, PR 13-24	162	161	1	68	71	23	95	60
	Arm 2: TVR + PR 1-12, PR 13-48	160	160	20	66	76	36	83	62
	Arm 3: TVR + PR 1-12, PR 13-48	118	117	12	38	61	31	55	47
Afdhal et al., 2014, ION-1, NCT01701401	Arm 1: SOF + LDV 1-12	214	169	0	0	24		11	16
	Arm 2: SOF + LDV + R 1-12	217	185	0	25	37		22	21
	Arm 3: SOF + LDV 1-24	217	178	4	0	29		8	16
	Arm 4: SOF + LDV + R 1-24	217	200	6	22	32		20	27
Afdhal et al., 2014, ION-2, NCT01768286	Arm 1: SOF + LDV 1-12	109	73	0	0	13		5	2
	Arm 2: SOF + LDV + R 1-12	111	96	0	9	20		10	11
	Arm 3: SOF + LDV 1-24	109	88	0	1	7		2	6
	Arm 4: SOF + LDV + R 1-24	111	100	0	12	25		10	16
Kowdley et al., 2014, ION-3, NCT01851330	Arm 1: SOF + LDV 1-8	215	145	0	2	15		2	3
	Arm 2: SOF + LDV + R 1-8	216	165	1	17	38		16	19
	Arm 3: SOF + LDV 1-12	216	149	2	2	24		5	5
Naggie et al., 2015, ION-4, NCT02073656	Arm 1: SOF + LDV 1-12	335	257	0		33			
Kawakami et al., 2014, UMIN 000006758	Arm 1: TVR + PR 1-12, PR 13-24	26		3	26				11
	Arm 2: TVR + PR 1-12, PR 13-24	26		4	26				13

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
Kumada et al., 2012[3]	Arm 1: TVR + PR 1-12, PR 13-24	126	126	21	115	32		23	48
	Arm 2: PR 1-48	63	63	14	46	7		13	18
Lai et al., 2016, NCT02021643	Arm 1: SOF + R 1-12	10	7	0	1				
	Arm 2: SOF + R 1-16	11	5	0	1				
	Arm 3: SOF + R 1-24	10	8	1	1				
Lawitz et al., 2015	Arm 1: SOF + PR 1-12	47	45	4	14	8	11		7
Lim at al., 2015, NCT02021656	Arm 1: SOF + LDV 1-12	178		2					
Lawitz et al., 2014, LONESTAR, NCT01726517	Arm 1: SOF + LDV 1-8	20	9	0	0	2		0	
	Arm 2: SOF + LDV + R 1-8	21	12	0	2	2		0	
	Arm 3: SOF + LDV 1-12	19	8	0	0	1		0	
	Arm 4: SOF + LDV 1-12	19	7	0	0	0		1	
	Arm 5: SOF + LDV + R 1-12	21	12	0	6	4		0	
Dore et al., 2016, MALACHITE-I, NCT01854697	Arms 1 & 3: OMB + PAR/r + DAS + R 1-12	153	115	1	10	32	0	19	12
	Arms 2 & 5: TVR + PR 1-12, PR 13-24 or PR 13-48	75	74	6	34	30	14	26	17
	Arm 4: OMB + PAR/r + DAS 1-12	83	41	0	1	7	0	5	0
Dore et al., 2016, MALACHITE-II, NCT01854528	Arm 1: OMB + PAR/r + DAS + R 1-12	101	63	0	3	10	1	13	3
	Arm 2: TVR + PR 1-12, PR 13-24 or PR 13-48	47	43	5	16	20	12	19	12
Marcellin et al., 2011, NCT00528528	Arm 1: TVR + PR 1-12, PR 13-24 or PR 13-48	40	40	3	18	18	2	19	29
	Arm 2: TVR + PR 1-12, PR 13-24 or PR 13-48	42	41	2	14	14	2	23	24
	Arm 3: TVR + PR 1-12, PR 13-24 or PR 13-48	40	40	4	18	16	0	20	23
	Arm 4: TVR + PR 1-12, PR 13-24 or PR 13-48	39	39	4	20	23	1	25	22

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
Bernabucci et al., 2014, MEN_BOC, NCT01457937	Arm 1: PR 1-4, BOC + PR 5-48 or PR 1-4, BOC + PR 5-36 or BOC + PR 5-36, PR 37-48	56		6	23	24			6
Mizokami et al., 2015, NCT01975675	Arm 1: SOF + LDV 1-12	171	112	0	3	5		6	5
	Arm 2: SOF + LDV + R 1-12	170	128	2	23	9		13	14
Lawitz et al., 2015, NAVIGATOR, NCT01458535	Arms 1a & 1b: OMB + PAR/r + R 1-12	30	26	0		10			
	Arms 2a & 2b: OMB + PAR/r 1-12	31	28	1		5			
Ogawa et al., 2013, UMIN 000011105	Arm 1: TVR + PR 1-12, PR 13-24	102		13	52		23		
Buti et al., 2014, OPTIMIZE, NCT01241760	Arm 1: TVR + PR 1-12, PR 13-24 or PR 13-48	369	360	57	157	128	30	159	129
	Arm 2: TVR + PR 1-12, PR 13-24 or PR 13-48	371	367	69	151	142	36	157	132
Oze et al., 2015, UMIN 000007313; UMIN 000007330	Arm 1: TVR + PR 1-12, PR 13-24								
	Arm 2: TVR + PR 1-12, PR 13-24								
Sulkowski et al., 2013, P05411 AM4, NCT00959699	Arm 1: PR 1-48	34	34	3	9	11	2	3	0
	Arm 2: PR 1-4, BOC + PR 5-48	64	63	13	26	26	12	12	5
Hezode et al., 2015, PEARL-1, NCT01685203	Arm 1: OMB + PAR/r 1-12	44	34	0		4		2	
	Arm 2: OMB + PAR/r + R 1-12	42	37	0		7		1	
	Arm 3: OMB + PAR/r + R 1-12	49	43	0		6		5	
Lawitz et al., 2015, PEARL-1, NCT01685203	Arm 4: OMB + PAR/r 1-12	42	31	0		8		6	
	Arm 5: OMB + PAR/r 1-12	40	32	0		0		0	
	Arm 6: OMB + PAR/r 1-24	47	38	3		5		8	

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
	Arm 7: OMB + PAR/r 1-24	52	38	0		5		8	
Andreone et al., 2014, PEARL-2, NCT01674725	Arm 1: OMB + PAR/r + DAS + R 1-12	91	72	2	10	19		13	8
	Arm 2: OMB + PAR/r + DAS 1-12	95	72	0	0	6		8	1
Ferenci et al., 2014, PEARL-3, NCT01767116	Arm 1: OMB + PAR/r + DAS + R 1-12	210	168		14	23		25	12
	Arm 2: OMB + PAR/r + DAS 1-12	209	140		1	9		11	8
Ferenci et al., 2014, PEARL-4, NCT01833533	Arm 1: OMB + PAR/r + DAS + R 1-12	100	92		5	21		10	5
	Arm 2: OMB + PAR/r + DAS 1-12	205	169		0	28		12	11
Pearlman et al., 2015, NCT02168361	Arm 1: SMV + SOF 1-12	58	46	0		6		6	10
	Arm 2: SOF + PR 1-12	24	22	3		7		4	3
Sulkowski et al., 2014, PHOTON-1, NCT01667731	Arm 1: SOF + R 1-24	114		3	13	18		6	7
	Arm 2: SOF + R 1-12	68		3	6	12		6	3
	Arm 3: SOF + R 1-24	41		1	3	6		2	4
Molina et al., 2015, PHOTON-2, NCT01783678	Arms 1, 2 & 4: SOF + R 1-24	200	182	5	16	32		5	15
	Arms 3 & GT2: SOF + R 1-24	55	47	1	3	4		3	3
Fried et al., 2013, PILLAR, NCT00882908	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	78	77	4	15	26	15	25	21
	Arm 2: SMV + PR 1-24 or SMV + PR 1-24, PR 25-48	75	75	1	16	16	23	17	10
	Arm 3: SMV + PR 1-12, PR 13-24 or PR 13-48	77	76	4	17	20	19	30	16
	Arm 4: SMV + PR 1-24 or SMV + PR 1-24, PR 25-48	79	79	2	15	24	18	24	18
	Arm 5: PR 1-48	77	75	4	16	21	16	35	18
Pol et al., 2015	Arm 1: SOF + PR 1-12	80	71	0	11	19	18	12	12

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
Merck & Co, 2016, PN077, NCT02358044	Arm 1: GZR + EBR 1-12	129	67	1	1	8	0	2	
	Arm 2: SOF + PR 1-12	126	117	1	16	13	11	8	
Jacobson et al., 2013, POSITRON, NCT01542788	Arm 1: Placebo	71	55	3		13		6	6
	Arm 2: SOF + R 1-12	207	184	4		46		23	18
Jacobson et al., 2013, FUSION, NCT01604850	Arm 1: SOF + R 1-12	103	92	1		22		12	7
	Arm 2: SOF + R 1-16	98	86	0		20		7	12
Forns et al., 2014, PROMISE, NCT01281839	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	260	253	6	44	59	46	72	60
	Arm 2: PR 1-48	133	125	7	27	26	29	37	30
Lawitz et al., 2013, PROTON, NCT01188772	Arm 1: SOF + PR 1-12, PR 13-24 or PR 13-48	48	47	2	11	15	8	8	13
	Arm 2: SOF + PR 1-12, PR 13-24 or PR 13-48	47	46	3	8	21	14	5	12
	Arm 3: PR 1-48	26	26	3	5	9	5	3	4
	Arm 4: SOF + PR 1-12	25	24	0	3	12	6	3	3
McHutchison et al., 2009, PROVE1, NCT00336479	Arm 1: TVR + PR 1-12, PR 13-24	79	79	18					
	Arm 2: TVR + PR 1-12, PR 13-48	79	79	11					
	Arm 3: TVR + PR 1-12	17	17	4					
	Arm 4: PR 1-48	75	75	8					
Hezode et al., 2009, PROVE2, NCT00372385	Arm 1: TVR + PR 1-12, PR 13-24	81	80	11	22	39	14	41	40
	Arm 2: TVR + PR 1-12	82	82	9	15	39	3	52	36
	Arm 3: TVR + P 1-12	78	78	7	7	24	6	46	37
	Arm 4: PR 1-36	82	81	6	14	33	2	29	29
McHutchison et al.,	Arm 1: TVR + PR 1-12, PR 13-24	115	112	11	30	41	12	39	58

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
2010, PROVE3, NCT00420784	Arm 2: TVR + PR 1-24, PR 25-48	113	112	29	30	54	11	50	68
	Arm 3: TVR + P 1-24	111	105	10	9	27	8	40	46
	Arm 4: PR 1-48	114	111	5	9	39	7	17	23
Vierling et al., 2014, PROVIDE, NCT00910624	Arm 1a: PR 1-4, BOC + PR 5-44 or BOC + PR 1-44	52	50	2					
	Arm 1b: PR 1-4, BOC + PR 5-44 or BOC + PR 1-44	85	82	6					
	Arm 1c: PR 1-4, BOC + PR 5-44 or BOC + PR 1-44	29	28	6					
Jacobson et al., 2014, QUEST-1, NCT01289782	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	264	255	7	53	65	64	79	89
	Arm 2: PR 1-48	130	125	3	27	32	23	26	42
Manns et al., 2014, QUEST-2, NCT01290679	Arm 1: SMV + PR 1-12, PR 13-24 or PR 13-48	257	249	2	53	63	54	66	69
	Arm 2: PR 1-48	134	132	0	37	24	36	36	27
Zeuzem et al., 2011, REALIZE, NCT00703118	Arm 1: TVR + PR 1-12, PR 13-48	266	260	39	79	94	38	138	99
	Arm 2: PR 1-4, TVR + PR 5-16, PR 17-48	264	260	29	94	87	35	132	95
	Arm 3: PR 1-48	132	126	4	20	31	14	36	25
Bacon et al., 2011, RESPOND-2, NCT00708500	Arm 1: PR 1-48	80	77	2	16	30		14	
	Arm 2: PR 1-4, BOC + PR 5-36 or BOC + PR 5-36, PR 37-48	162	160	13	70	71		30	
	Arm 3: PR 1-4, BOC + PR 5-48	161	161	20	74	63		31	
Moreno et al., 2015, RESTORE, NCT01567735	Arms 1a, 1b, 1c & 1d: SMV + PR 1-12, PR 13-24 or PR 13-48	107	105	0	11		5	22	15
Rodriguez-Torres et al., 2015, NCT01565889	Arm 1: SOF + PR 1-12	23	16	2	12		4		
Ruane et al., 2015,	Arm 1: SOF + R 1-12	31	28	0	0			7	1

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
NCT01713283	Arm 2: SOF + R 1-24	29	29	0	3			7	9
Feld et al., 2014, SAPPHIRE-1, NCT01716585	Arm 1: OMB + PAR/r + DAS + R 1-12	473	414	3	25	112		80	51
	Arm 2: Placebo 1-12, OMB + PAR/r + DAS + R 13-24	158	116	1	0	21		6	9
Zeuzem et al., 2014, SAPPHIRE-2, NCT01715415	Arm 1: OMB + PAR/r + DAS + R 1-12	297	271	3	16	60		41	26
	Arm 2: Placebo 1-12, OMB + PAR/r + DAS + R 13-24	97	80	0	0	17		5	6
Bourliere et al., 2015, SIRIUS, NCT01965535	Arm 1: SOF + LDV + R 1-12	77	74	1		14		22	5
	Arm 2: SOF + LDV 1-24	78	68	0		8		7	2
Charlton et al., 2015, SOLAR-1, NCT01938430	Arm 1: SOF + LDV 1-12	30	29	0					
	Arm 2: SOF + LDV 1-24	29	28	2					
	Arm 3: SOF + LDV 1-12	23	23	1					
	Arm 4: SOF + LDV 1-24	26	26	2					
	Arm 5: SOF + LDV 1-12	55	55	0					
	Arm 6: SOF + LDV 1-24	56	55	2					
	Arm 7: SOF + LDV 1-12	26	25	1					
	Arm 8: SOF + LDV 1-24	25	24	0					
	Arm 9: SOF + LDV 1-12	26	25	2					
	Arm 10: SOF + LDV 1-24	26	26	3					
	Arm 11: SOF + LDV 1-12	5	5	0					
	Arm 12: SOF + LDV 1-24	4	4	0					
	Arm 13: SOF + LDV 1-12	4	4	0					
	Arm 14: SOF + LDV 1-24	2	2	0					

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
Osinusi et al., 2013, SPARE, NCT01441180	Arm 1: SOF + R 1-24	10	9	0	4	1		0	1
	Arm 2: SOF + R 1-24	25	24	0	8	4		2	0
	Arm 3: SOF + R 1-24	25	21	0	4	5		0	0
Kwo et al., 2010, SPRINT-1, NCT00423670	Arm 1: PR 1-48	104	102	8	35	45	12	16	6
	Arm 2: PR 1-4, BOC + PR 5-28	103	102	15	55	42	17	19	6
	Arm 3: PR 1-4, BOC + PR 5-48	103	102	9	58	48	31	19	9
	Arm 4: BOC + PR 1-28	107	106	12	60	41	25	19	3
	Arm 5: BOC + PR 1-48	103	103	20	54	56	26	23	9
	Arm 6: BOC + PR 1-48	16	16	4	10	10	3	1	1
	Arm 7: BOC + PR 1-48	59	59	7	14	35	19	11	1
Poordad et al., 2011, SPRINT-2, NCT00705432	Arm 1: PR 1-48	363	356	57	107	153	77	98	83
	Arm 2: PR 1-4, BOC + PR 5-28 or BOC + PR 5-28, PR 29-48	368	365	45	182	175	92	87	93
	Arm 3: PR 1-4, BOC + PR 5-48	366	364	60	179	159	93	94	88
Kohli et al., 2015a, SYNERGY, NCT01805882	Arm 1: SOF + LDV 1-12	20	20	0		1			3
Kohli et al., 2015b, SYNERGY, NCT01805882	Arm 2: SOF + LDV 1-12	21	10	0		2			
Osinusi et al., 2014, SYNERGY, NCT01805882	Arm 3: SOF + LDV 1-12	14		0		0		0	
Wilson et al., 2016, SYNERGY, NCT01805882	Arm 4: SOF + LDV 1-12	34	30	0					

Citation(s), trial name, registration number	Treatment arms	Arm (N)	OAE (n)	DAE (n)	Anemia (n)	Nausea (n)	Neutropenia (n)	Pruritus (n)	Rash (n)
Cotte et al., 2014, TelapreVIH, NCT01332955	Arm 1: PR 1-4, TVR + PR 5-16, PR 17-48 or PR 17-72	69		14	46	16		32	
Reau et al., 2015, TOPAZ-II, NCT02167945	Arm 1: OMB + PAR/r + DAS ± R 1-12/1-24	615	492	6		99		78	
Sulkowski et al., 2015, TURQUOISE-I, NCT01939197	Arm 1: OMB + PAR/r + DAS + R 1-12	31	28	0		5		6	
	Arm 2: OMB + PAR/r + DAS + R 1-24	32	28	0		6		2	
Poordad et al., 2014, TURQUOISE-II, NCT01704755	Arm 1: OMB + PAR/r + DAS + R 1-12	208	191	4	16	37	37	10	23
	Arm 2: OMB + PAR/r + DAS + R 1-24	172	156	4	18	35	35	12	25
Feld et al., 2016, TURQUOISE-III, NCT02219503	Arm 1: OMB + PAR/r + DAS 1-12	60	46	0				6	
Zeuzem et al., 2014, VALENCE, NCT01682720	Arm 1: SOF + R 1-12	84	72	1	5	26		20	1
	Arm 2: SOF + R 1-24	250	229	1	15	33		67	24
Sulkowski et al., 2013, VX08-950-110, NCT00983853	Arms 1, 3 & 5: TVR + PR 1-12, PR 13-48	38	38	3	5	13	9	13	11
	Arms 2, 4 & 6: PR 1-48	22	22	0	4	5	5	1	4
Walsh et al., 2015, NCT02120300	Arms 1, 2 & 3: SOF + LDV 1-12, SOF + LDV 1-24, SOF + R 1-12								
Wyles et al., 2015, NCT01987453	Arm 1: SOF + LDV + R 1-12	51	41	1		5		3	6

A7. **Priority question**: Please provide the following:

a. All results (SVR and AEs) for the 12 subgroups (that is, by genotype, treatment history and cirrhosis status) for all treatment arms for the MSD studies.

Please note that these data can be found in Appendix 9 within the MSD UK_ID842 Appendices 1-23 document. The relevant sections of these tables have been replicated below.

Sustained virologic response for MSD studies

Genotype 1a, treatment-naïve, without cirrhosis

Regimen	Citation(s), trial name, reg number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	123	112 (91)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	123	118 (96)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	7	7 (100)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	40	40 (100)
Arm 6: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	30	29 (97)
Arm 16: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	22	19 (86)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	122	117 (96)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077, NCT02358044	14	14 (100)

Genotype 1a, treatment-naïve, with cirrhosis

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	32 (94)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	19	19 (100)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	3 (100)
Arm 8: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	20	19 (95)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	28	26 (93)

Genotype 1a, treatment-experienced, without cirrhosis

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	40	36 (90)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	1 (100)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	6	6 (100)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	10 (91)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077, NCT02358044	4	4 (100)

Genotype 1a, treatment-experienced, with cirrhosis

Regimen	Citation(s), trial name, reg number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	21	19 (90)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	2	2 (100)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	10 (91)

Genotype 1b, treatment-naïve, without cirrhosis

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	97	95 (98)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	32	30 (94)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	1 (100)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	41	41 (100)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	13	12 (92)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	24	22 (92)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077, NCT02358044	64	63 (98)

Genotype 1b, treatment-naïve, with cirrhosis

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	34 (100)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	12	12 (100)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	1 (100)
Arm 8: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	7	7 (100)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	6	6 (100)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077, NCT02358044	18	18(100)

Genotype 1b, treatment-experienced, without cirrhosis

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	25	25 (100)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	11	10 (91)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	8	7 (88)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077, NCT02358044	19	19(100)

Genotype 1b, treatment-experienced, with cirrhosis

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	9	9 (100)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	3	3 (100)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077, NCT02358044	4	4(100)

Genotype 4, treatment-naïve, without cirrhosis

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SCAPE, NCT01932762	10	7 (70)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	16	16 (100)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	24	23 (96)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077, NCT02358044	4	4(100)

Genotype 4, treatment-naïve, with cirrhosis

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	2	2 (100)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	4	4 (100)

Genotype 4, treatment-experienced, without cirrhosis

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	3	3 (100)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077, NCT02358044	2	2(100)

Genotype 4, treatment-experienced, with cirrhosis

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with SVR, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	6	4 (67)

Safety outcomes values used within the NMA

Genotype 1, without cirrhosis; OAE

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with OAE, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	125	91 (73)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	32	24 (75)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	124	104 (84)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	24	20 (83)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	40	27 (68)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	25	14 (56)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	123	89 (72)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	97	64 (66)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	9	7 (78)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	41	32 (78)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	1 (100)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	6	4 (67)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	1 (100)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	46	35 (76)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	11	7 (64)
Arm 6: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	30	26 (87)
Arm 16: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	22	14 (64)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	10 (91)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	12	11 (92)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	8	5 (63)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	14	8 (57)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	2 (50)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	64	33 (52)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	19	9 (47)

Genotype 1, without cirrhosis, DAE

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with DAE, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	125	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	32	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	124	1 (1)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	24	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	40	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	25	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	123	1 (1)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	97	1 (1)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	9	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	41	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	6	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	46	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	11	0 (0)
Arm 6: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	30	0 (0)
Arm 16: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	22	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	0 (0)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	12	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	8	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	14	1 (7)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	64	0 (0)

Genotype 1, without cirrhosis Anemia

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with anemia, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	125	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	32	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	124	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	24	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	40	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	25	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	123	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	97	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	9	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	41	1 (2)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	6	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	46	1 (2)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	11	0 (0)
Arm 6: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	30	0 (0)
Arm 16: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	22	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	0 (0)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	12	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	8	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	14	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	64	1 (2)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	19	0 (0)

Genotype 1, without cirrhosis Nausea

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with nausea, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	125	13 (10)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	32	4 (13)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	124	14 (11)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	24	1 (4)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	40	3 (8)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	25	4 (16)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	123	15 (12)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	97	9 (9)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	9	1 (11)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	41	7 (17)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	6	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	46	7 (15)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	11	1 (9)
Arm 6: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	30	5 (17)
Arm 16: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	22	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	1 (9)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	12	2 (17)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	8	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	14	3 (21)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	64	4 (6)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	19	0 (0)

Genotype 1, without cirrhosis Neutropenia

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with neutropenia, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	125	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	32	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	124	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	24	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	40	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	25	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	123	1 (1)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	97	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	9	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	41	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	6	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	46	1 (2)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	11	0 (0)
Arm 6: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	30	0 (0)
Arm 16: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	22	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	0 (0)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	12	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	8	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	14	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	64	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	19	0 (0)

Genotype 1, without cirrhosis Pruritus

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with pruritus, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	125	3 (2)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	32	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	124	3 (2)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	24	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	40	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	25	1 (4)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	123	3 (2)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	97	1 (1)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	9	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	41	2 (5)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	6	1 (17)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	46	2 (4)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	11	1 (9)
Arm 6: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	30	0 (0)
Arm 16: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	22	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	2 (18)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	12	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	8	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	14	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	64	1 (2)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	19	1 (5)

Genotype 1, without cirrhosis Rash

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with rash, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	125	4 (3)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	32	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	124	2 (2)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	24	1 (4)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	40	1 (3)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	25	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	123	4 (3)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	97	1 (1)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	9	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	41	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	6	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	46	2 (4)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	11	0 (0)
Arm 6: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	30	1 (3)
Arm 16: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	22	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	1 (9)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	12	1 (8)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	8	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	14	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	64	2 (3)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	19	1 (5)

Genotype 1, with cirrhosis OAE

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with OAE, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	19	15 (79)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	12	12 (100)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	30	27 (90)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	6	5 (83)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	21	18 (86)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	9	7 (78)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	23 (68)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	15 (44)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	2 (67)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	3 (100)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	1 (100)
Arm 8: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	20	11 (55)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	10 (91)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	7	6 (86)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	3	1 (33)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	18	8 (44)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	2 (50)

Genotype 1, with cirrhosis DAE

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with DAE, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	19	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	12	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	30	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	6	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	21	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	9	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	1 (3)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 8: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	20	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	0 (0)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	7	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	18	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 1, with cirrhosis Anemia

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with anemia, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	19	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	12	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	30	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	6	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	21	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	9	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	1 (3)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 8: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	20	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	0 (0)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	7	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	18	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 1, with cirrhosis Nausea

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with nausea, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	19	2 (11)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	12	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	30	5 (17)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	6	1 (17)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	21	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	9	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	2 (6)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	1 (33)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	1 (33)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 8: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	20	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	1 (9)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	7	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	18	1 (6)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 1, with cirrhosis Neutropenia

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with neutropenia, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	19	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	12	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	30	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	6	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	21	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	9	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	1 (3)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 8: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	20	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	0 (0)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	7	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	18	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 1, with cirrhosis Pruritus

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with pruritus, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	19	2 (11)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	12	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	30	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	6	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	21	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	9	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	2 (6)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	1 (3)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 8: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	20	1 (5)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	0 (0)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	7	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	18	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 1, with cirrhosis Rash

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with rash, n (%)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	19	1 (5)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	12	0 (0)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	30	2 (7)
Arm 1: EBR/GZR 1-12	Dore et al., 2015, C-EDGE CO-STAR, NCT02105688	6	0 (0)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	21	1 (5)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	9	1 (11)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	2 (6)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	34	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	0 (0)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	3	1 (33)
Arm 2: EBR/GZR 1-12	Merck & Co, 2015, C-SURFER, NCT02092350	1	0 (0)
Arm 8: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	20	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	11	1 (9)
Arm 3: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	7	0 (0)
Arm 12: EBR/GZR 1-12	Merck & Co, 2015, C-WORTHY, NCT01717326	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	18	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 4, without cirrhosis OAE

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with OAE, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	3	2 (67)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	2	2 (100)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SCAPE, NCT01932762	10	9 (90)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	16	14 (88)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	24	14 (58)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	3 (75)

Genotype 4, without cirrhosis DAE

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with DAE, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	2	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SCAPE, NCT01932762	10	1 (10)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	16	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	24	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 4, without cirrhosis Anemia

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with anemia, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	2	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SCAPE, NCT01932762	10	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	16	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	24	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 4, without cirrhosis Nausea

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with nausea, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	2	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SCAPE, NCT01932762	10	1 (10)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	16	2 (13)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	24	1 (4)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 4, without cirrhosis Neutropenia

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with neutropenia, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	2	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SCAPE, NCT01932762	10	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	16	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	24	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 4, without cirrhosis Pruritus

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with pruritus, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	2	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SCAPE, NCT01932762	10	1 (10)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	16	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	24	1 (4)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 4, without cirrhosis Rash

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with rash, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	3	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	2	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-SCAPE, NCT01932762	10	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	16	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	24	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2016, PN077	4	0 (0)

Genotype 4, with cirrhosis OAE

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with OAE, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	6	5 (83)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	2	2 (100)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	4	3 (75)

Genotype 4, with cirrhosis DAE

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with DAE, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	6	1 (17)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	2	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	4	0 (0)

Genotype 4, with cirrhosis Anemia

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with anemia, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	6	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	2	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	4	0 (0)

Genotype 4, with cirrhosis Nausea

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with nausea, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	6	2 (33)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	2	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	4	0 (0)

Genotype 4, with cirrhosis Neutropenia

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with neutropenia, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	6	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	2	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	4	0 (0)

Genotype 4, with cirrhosis Pruritus

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with pruritus, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	6	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	2	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	4	0 (0)

Genotype 4, with cirrhosis Rash

Regimen	Citation(s), trial name, registration number	Patients randomised	Patients with rash, n (%)
Arm 1: EBR/GZR 1-12	Kwo et al., 2015, C-EDGE TE, NCT02105701	6	0 (0)
Arm 1: EBR/GZR 1-12	Merck & Co, 2015, C-EDGE TN, NCT02105467	2	0 (0)
Arm 1: EBR/GZR 1-12	Rockstroh et al., 2015, C-EDGE CO-INFECTION, NCT02105662	4	0 (0)

b. All SVR results for the 4 subgroups as defined for the network meta-analysis of AEs (that is, GT1, with/without cirrhosis; and GT4, with/without cirrhosis) for the MSD studies.

Please see below. These have been calculated from the values presented in Appendix 9.

Table 1: Sustained viral responses by genotype and cirrhosis status in MSD studies

Trial Name	Genotype 1		Genotype 4	
	No cirrhosis – SVR12 (%)	Cirrhosis – SVR12 (%)	No cirrhosis – SVR12 (%)	Cirrhosis – SVR12 (%)
C-WORTHY	84/77 (91.7)	41/39 (95.1)	-	-
C-SCAPE	-	-	10/7 (70.0)	-
C-SURFER	107/106 (99.1)	6/6 (100.0)	-	-
C-EDGE TN	220/207 (94.1)	68/66 (97.1)	16/16 (100.0)	2/2 (100.0)
C-EDGE CO-INFECTION	155/148 (95.5)	31/31 (100.0)	24/23 (95.8)	4/4 (100.0)
C-EDGE CO-STAR	146/139 (95.2)	34/32 (94.1)	-	-
C-EDGE TE	65/61 (93.8)	30/28 (93.3)	3/3 (100.0)	6/4 (66.7)
PN077	101/100 (99.0)	22/22 (100.0)	6/6 (100.0)	-
Total	**878/838 (95.4)**	**232/224 (96.6)**	**59/55 (93.2)**	**12/10 (83.3)**

SVR12, sustained viral response

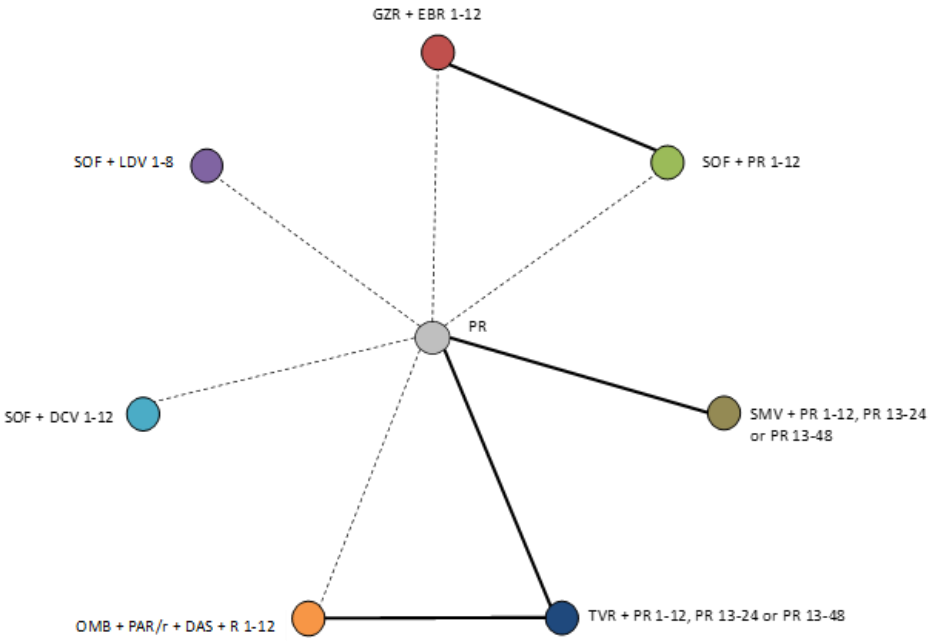
A8. **Priority question**: The WinBUGS code used for the network meta-analysis was provided but the corresponding data are missing.

a. Please provide the data used in each network meta-analysis and highlight which control arms have been imputed as reported in Section 4.10.12 of the company submission.

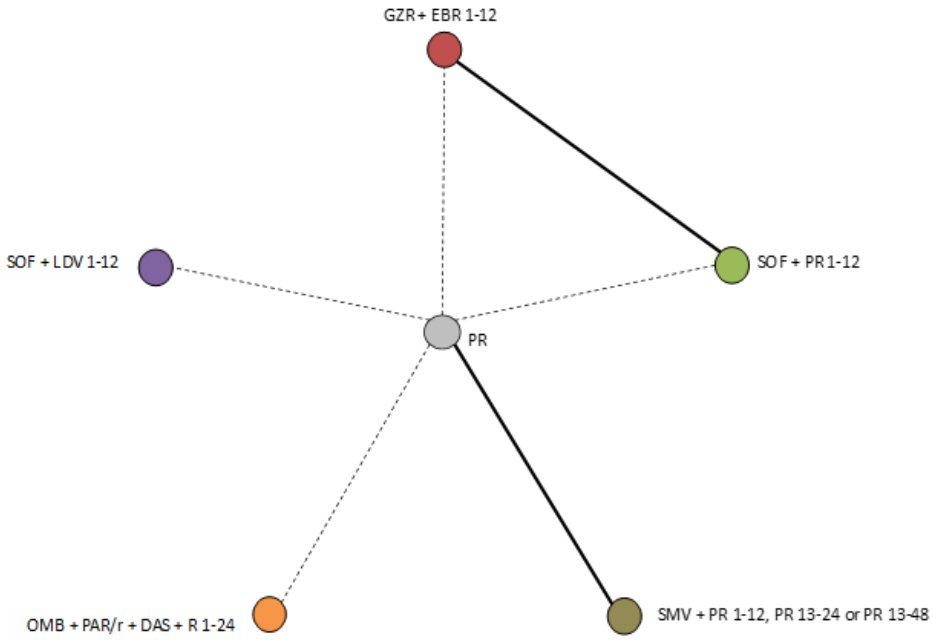
All inputs used in the NMA are reported in Appendix 9 (pages 199-244) of the MSD UK_ID Appendices 1-23 document. Figures 1-6 show the networks of evidence in each analysis, with dashed lines indicating where control arms were imputed.

Figure 1: Network of evidence for analysis of SVR in genotype 1a patients who are treatment-naïve.

a. Without cirrhosis



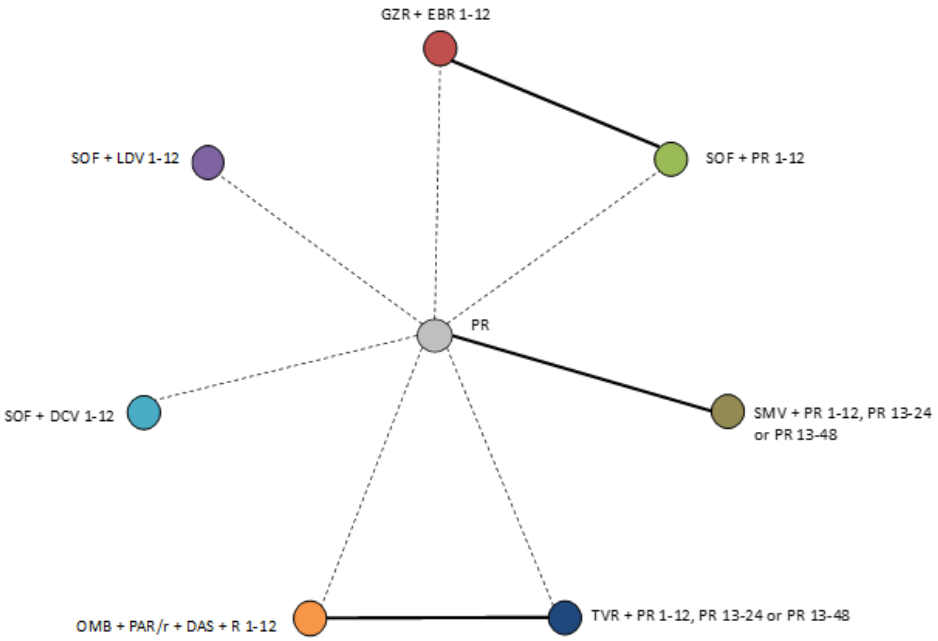
b. With cirrhosis



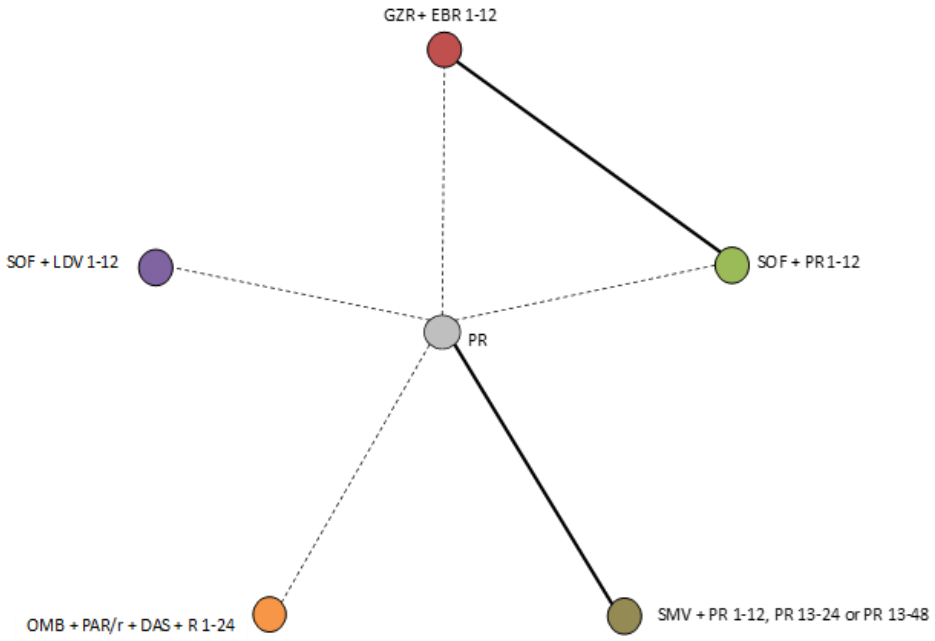
Note: Solid lines represent where head-to-head comparisons exist, with dotted lines representing imputed control arms.
DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TVR, telaprevir.

Figure 2: Network of evidence for analysis of SVR in genotype 1a patients who are treatment-experienced.

a. Without cirrhosis



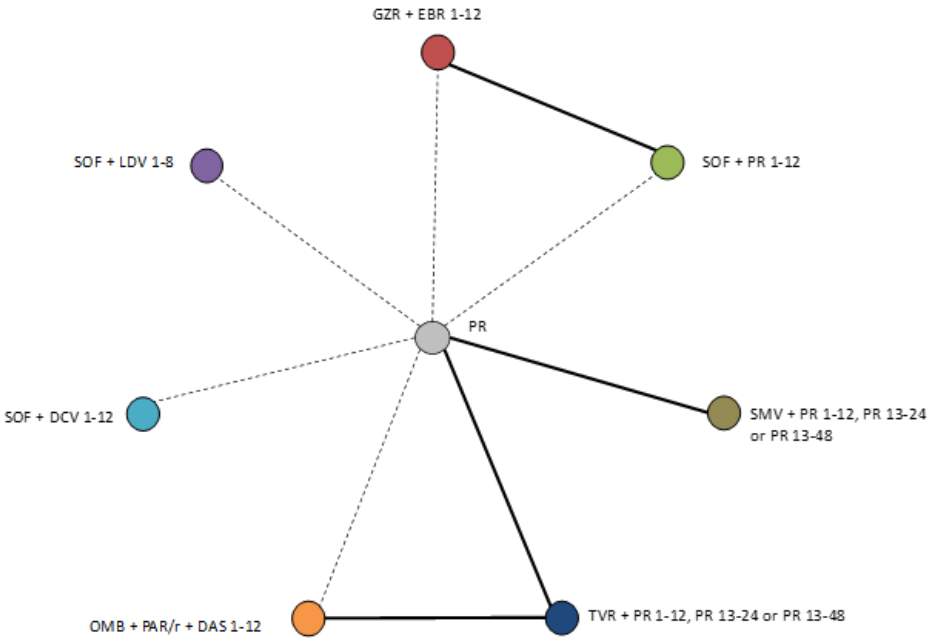
b. With cirrhosis



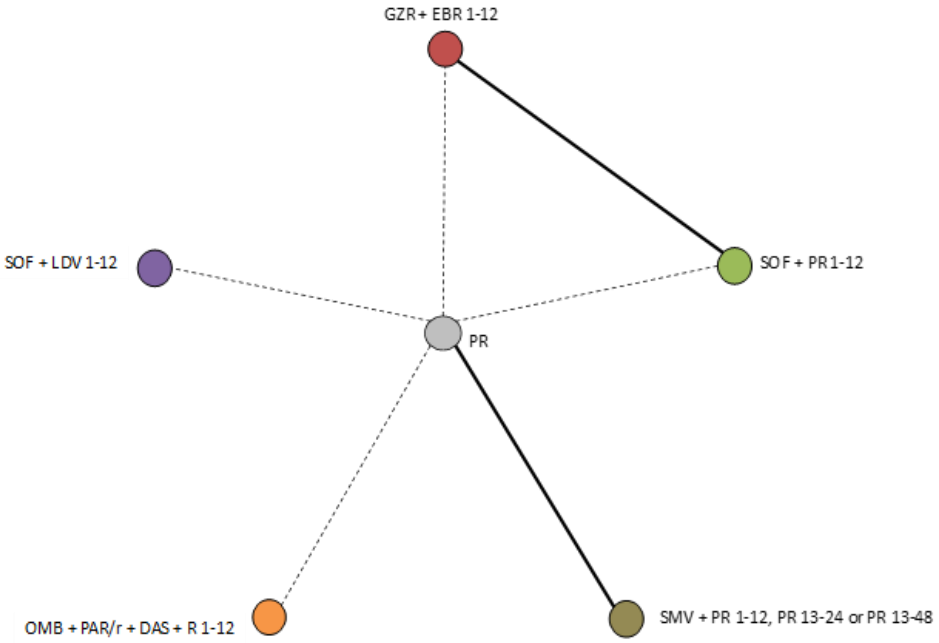
Note: Solid lines represent where head-to-head comparisons exist, with dotted lines representing imputed control arms.
DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TVR, telaprevir.

Figure 3: Network of evidence for analysis of SVR in genotype 1b patients who are treatment-naïve.

a. Without cirrhosis



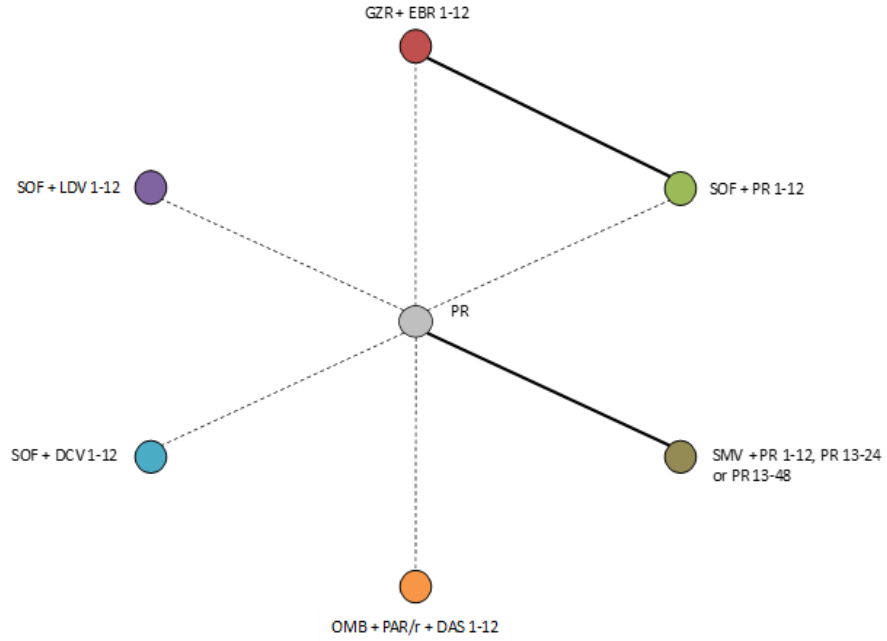
b. With cirrhosis



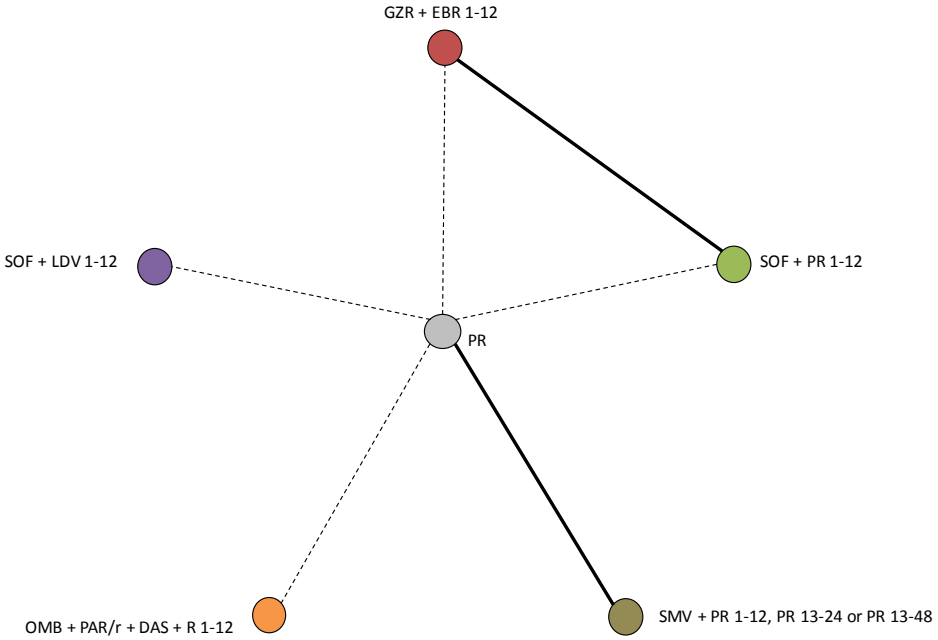
Note: Solid lines represent where head-to-head comparisons exist, with dotted lines representing imputed control arms.
DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TVR, telaprevir.

Figure 4: Network of evidence for analysis of SVR in genotype 1b patients who are treatment-experienced.

a. without cirrhosis



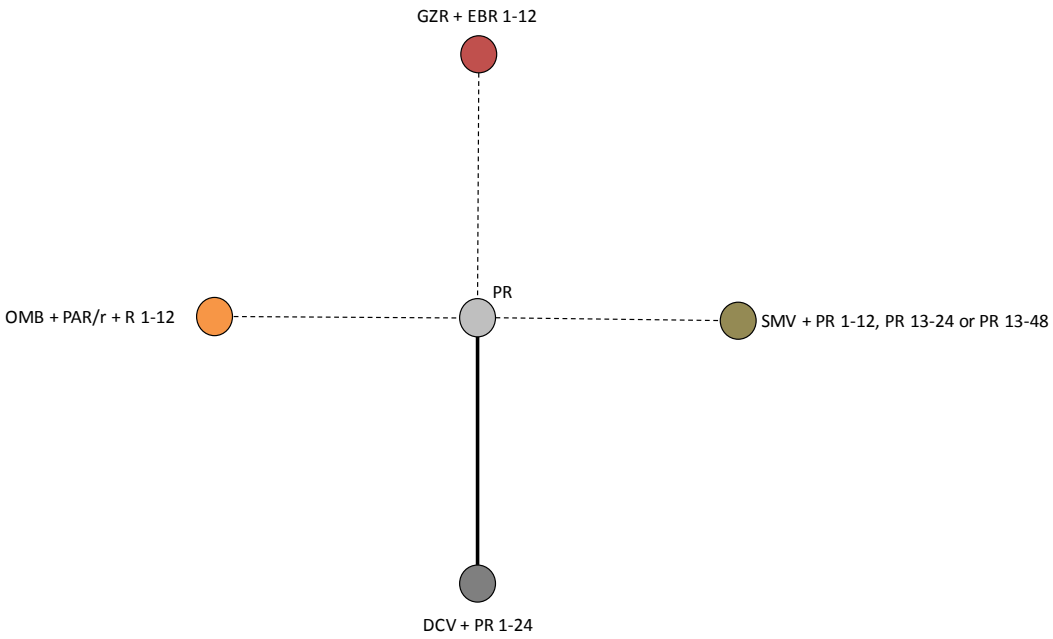
b. with cirrhosis



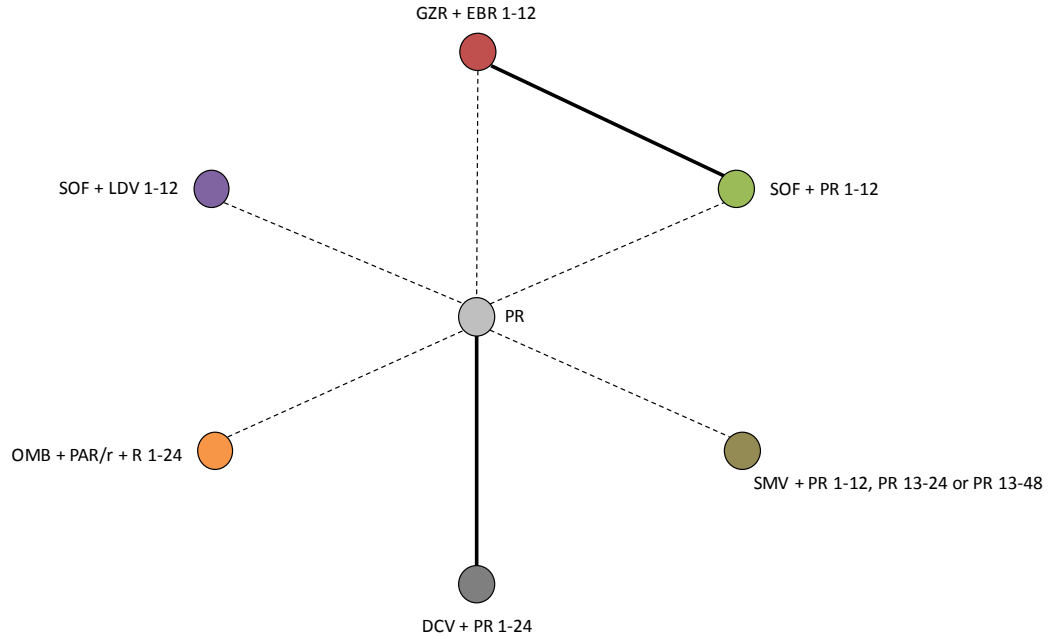
Note: Solid lines represent where head-to-head comparisons exist, with dotted lines representing imputed control arms.
DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TVR, telaprevir.

Figure 5: Network of evidence for analysis of SVR in genotype 4 patients who are treatment-naïve.

a. without cirrhosis



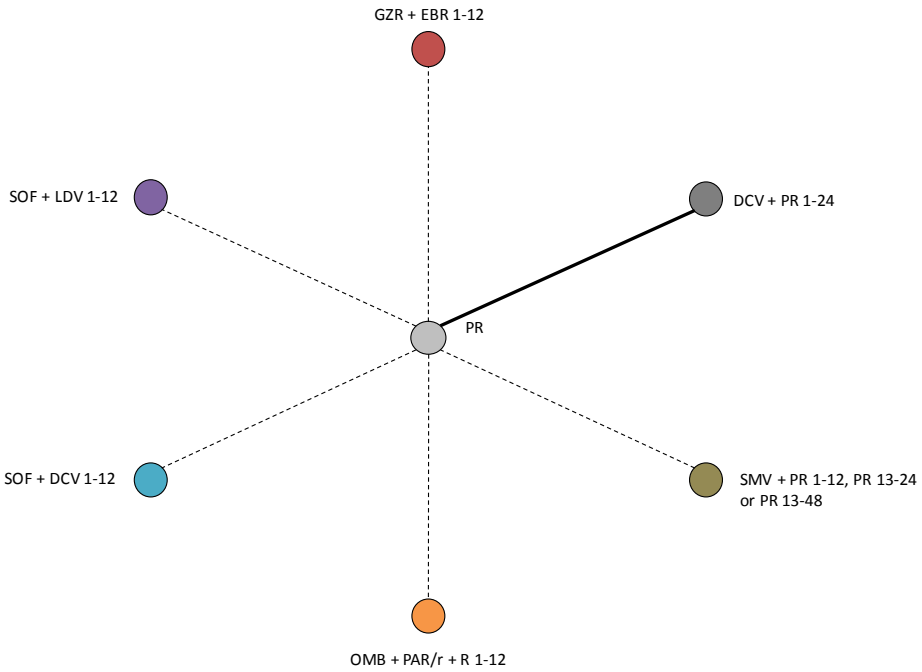
b. With cirrhosis



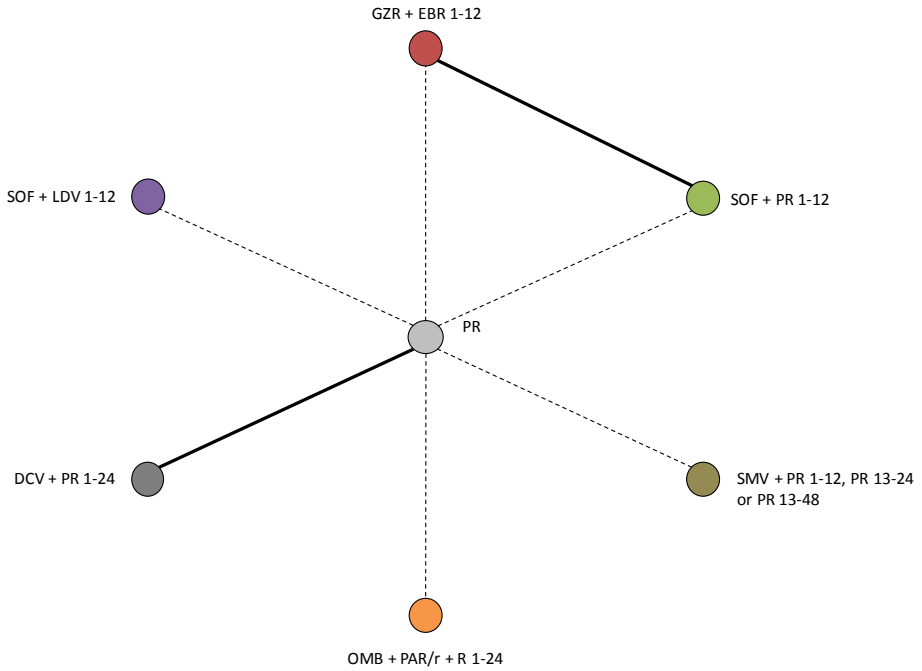
Note: Solid lines represent where head-to-head comparisons exist, with dotted lines representing imputed control arms.
DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TVR, telaprevir.

Figure 6: Network of evidence for analysis of SVR in genotype 4 patients who are treatment-experienced.

a. Without cirrhosis



b. With cirrhosis



Note: Solid lines represent where head-to-head comparisons exist, with dotted lines representing imputed control arms.
DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TVR, telaprevir.

b. Please also provide details of how the data were imputed for any missing comparator arms (e.g., full poster and the technical report for the analyses presented at ISPOR 2015 Milan [reference 106 in the company submission], statistical codes and data inputs used in creating the imputation as well as the outputs).

The code used to impute the control arms, along with an example of how this was implemented for the genotype 1a, treatment naïve, without cirrhosis subgroup, can be found below:

```
pr_model <- glm(cbind(r,N-r) ~ 1  ,family=binomial, data=pr_arms)
print(pr_model)
# predicted prob of control response inputed to ds_no_pr1
pred_prob <-predict(pr_model,ds_no_pr1,type="response")
ds_no_pr1 = data.frame(ds_no_pr1, pred_prob)
ds_no_pr1$r = round(ds_no_pr1$pred_prob*ds_no_pr1$N,0)
ds_no_pr1$p = ds_no_pr1$r/ds_no_pr1$N

# adjust N and r of non-PR arms in trials without PR
ds_no_pr$N=round(ds_no_pr$N/(ds_no_pr$na+1)*ds_no_pr$na,0)
ds_no_pr$r=round(ds_no_pr$r/(ds_no_pr$na+1)*ds_no_pr$na,0)
```

Four trials provided PR SVR response probabilities for the genotype 1a, treatment naïve, without cirrhosis subgroup:

$$SVR_{ADVANCE} = 151/340 = 0.444117647$$
$$SVR_{PILLAR} = 51/77 = 0.662337662$$
$$SVR_{QUEST-1} = 60/113 = 0.530973451$$
$$SVR_{QUEST-2} = 61/119 = 0.512605042$$

The crude r_x and N_x, where N is the total number of patients in the subgroup from trial x and r is the number of these patients who achieved SVR, were entered into a logistic regression, which resulted in a model with:

$$logit(p) = -0.009245058$$
$$\log(p/(1-p)) = -0.009245058$$
$$p/1-p = \exp(-0.009245058)$$

Where p is the probability of achieving an SVR. The final equation above further simplifies to:

$$p = \exp -0.009245058/1 + \exp(-0.009245058) = 0.497688752$$

This p was then used to create the imputed PR arm for those trials that did not include a PR control arm. Note that when creating the imputed control arms, the sample sizes in each non-comparative trial arm were reduced to avoid artificially increasing precision. For example, in a two arm trial in which the imputed arm is a third arm, the sample size from

each observed arm are reduced by a third and the imputed arm is set to the same size as the reduced arms. The number of cases is reduced by the same factor so as to conserve the probability of the event.

A9. In table 35 (pages 124 to 125 of the company submission), the trials included in the network meta-analysis of sustained viral response are listed.

a. Please explain why the ATOMIC, ION-1, PEARL-3, ELECTRON, LONESTAR, Mizokami and PEARL-1 trials are not included for GT1a/TX-Naive/No Cirrhosis (for instance: ATOMIC matches the inclusion criteria more closely than ALLY-2).

Data from ATOMIC[4] (SOF + PR 1-12) and LONESTAR[5] (SOF/LDV 1-8) were not used as the SVRs presented in their publications were not split by sub genotype. ION-1[6], ELECTRON[7], and Mizokami et al., 2015[8] did not assess a SOF regimen that is recommended for this patient group; SOF/LDV 1-8 is the recommended regimen for genotype 1 patients who are treatment naïve and without cirrhosis, while ELECTRON[7] only assessed SOF + PR 1-12 in genotypes 2 and 3. Finally, neither PEARL-I[9,10] (genotypes 1b and 4) nor PEARL-III[11] (genotype 1b) included genotype 1a patients.

b. Please explain why the Sulkowski, ADVANCE, ALLY-2, ATOMIC, ELECTRON, LONESTAR, PEARL-1 and Merck PN077 trials are not included for GT1a/TX-Naive/With Cirrhosis (for instance: ALLY-2 was included for "GT1a/TX-Naive/No Cirrhosis", but patients with mixed fibrosis status were included, so it could also be included here. The same applies to PN077).

As previously stated, the ITC statistical analysis plan restricted the PR data used in the imputation of control arms for each NMA to comparative trials featuring another intervention of interest. However, it did allow for the inclusion of comparative PR trials without an additional intervention of interest if they added to the robustness of the network. The only such case was in GT1a/TX-Naive/No Cirrhosis, where ADVANCE [12] provided a link between OMB + PAR/r + DAS 1-12 and PR 1-48 though a shared comparison with TVR + PR 1-12; PR 13-24 or PR 13-48 [13]. ADVANCE was not included in GT1a/TX-Naive/With Cirrhosis as none of the included trials featured a TVR + PR 1-12; PR 13-24 or PR 13-48 control arm. ELECTRON [7] was not included as it assessed SOF/LDV 1-12 in treatment-experienced patients with cirrhosis, and SOF + PR 1-12 in patients with genotype 2 and 3. Similarly, LONESTAR [5] was not included as it assessed SOF/LDV 1-12 in patients with cirrhosis who were also treatment-experienced. A1444040 [14] and ALLY-2 [15] were not included as SOF + DCV 1-12 is not recommended in patients with cirrhosis. PEARL-I [9,10] was not included because it did not include genotype 1a patients. Finally, PN077 [16] was not included as none of the genotype 1a patients in the arm had cirrhosis present. Please note that wherever

possible subgroup information was used that matched the exact subgroup of interest. For example, in GT1a/TX-Naive/No Cirrhosis the subgroup SVR from ALLY-2 [15] of 58/60 (Table 6 on page 34 of the supplementary material) was used, rather than the overall SVR from the entire arm that included patients of mixed fibrosis status and genotype (98/101).

c. Please provide the selection criteria for inclusion in all network meta-analyses for sustained viral response and adverse events.

As per section 4.1.3 in main submission, trial selection was decided according to hierarchical exclusion criteria (Table 20 on page 55 in the main submission). Included trials were then reviewed for comparators that have been recommended by NICE. Publications related to these trials were then checked to see whether they contained information on outcomes for subgroups of interest e.g. SVRs for GT1a, treatment-naïve, without cirrhosis. In the absence of specific subgroup information, assumptions were made to facilitate to comparisons with trials with data available. No trials were excluded based on risk of bias or because of the characteristics of patients at baseline, although the latter was explored through a sensitivity analysis.

A10. Please explain why the genotypes for the network meta-analysis of sustained viral response are split by subtype into GT1a and GT1b.

As per the draft SmPC included as appendix 1 of the submission, MSD presented data as per the anticipated label for Zepatier. Furthermore, previous recommendations by NICE had also included comparators, which had recommendations presented according to sub-genotype.

A11. Please provide full references and PDF documents for the following citations in the table of included studies in appendix 3.

10	Gane et al.	2013	Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis c
12	Hézode et al.	2014	Daclatasvir in Combination With Peginterferon Alfa-2a and Ribavirin for Treatment-Naive Patients With HCV Genotype 4 Infection: Phase 3 COMMAND-4 Results
14	Jacobson et al.	2011	Telaprevir for previously untreated chronic hepatitis c virus infection
22	Lawitz et al.	2013	Sofosbuvir for previously untreated chronic hepatitis c infection
45	Sulkowski et al.	2014	Daclatasvir plus sofosbuvir for previously treated or untreated chronic hcv infection

In addition to this document, please find the below references as PDF documents. These were mistakenly missed from the reference pack.

1. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide Polymerase Inhibitor Sofosbuvir plus Ribavirin for Hepatitis C. *N Engl J Med.* 2013;368(1):34-44.

2. Hézode C, Alric A, Brown A, et al. Daclatasvir in Combination With Peginterferon Alfa-2a and Ribavirin for Treatment-Naive Patients With HCV Genotype 4 Infection: Phase 3 COMMAND-4 Results. *IDWeek 2014.* 2014.

3. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. *N Engl J Med.* 2011;364(25):2405-2416.

4. Lawitz EM, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med.* 2013;368(20):1878-1887.

5. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Study Group. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection.[Erratum appears in N Engl J Med. 2014 Apr 10;370(15):1469]. *N Engl J Med.* 2014;370(3):211-221.

A12. **Priority question**: Table 69 (page 201 of the company submission): Please provide full HRQoL results for the elbasvir/grazoprevir comparative studies (C-CO-STAR, C-EDGE TN, C-SURFER and C-EDGE H2H), that is, baseline data, 12-week data, and change score (N, mean and SD) for all treatment arms, and a measure of the significance of the difference between arms (p-value or 95% CI).

The below tables report QoL data pulled together for each of the four comparative studies EBR/GZR 12 weeks at baseline, 12-week, and change score. EQ-5D scores are reported below for C-EDGE TN and C-EDGE H2H and SF-36 scores are reported for C-SURFER and C-COSTAR.

Please note that Hungarian patients have been excluded from the C-EDGE H2H QoL results provided in tables 3 and 4. This is due to a translation error in the administration of the EQ-5D questionnaires.

b) EQ-5D-5L scores

- C-EDGE TN (protocol number: 060):

Table 1. Summary of mean and mean change from baseline score for EQ-5D health utility scores over time (PRO FAS) EBR/GZR (12 weeks) in all patients

	All patients			
	N[†]	Mean, SD (95% CI)	N[‡]	Change from Baseline, SD (95% CI)
Baseline				
EQ5D-5L Score	313	0.82, 0.21 (0.79, 0.84)		
Week 4				
EQ5D-5L Score	306	0.82, 0.20 (0.79, 0.84)	303	0.00, 0.17 (-0.02, 0.02)
End of Treatment				
EQ5D-5L Score	309	0.82, 0.19 (0.80, 0.84)	309	-0.00, 0.17 (-0.02, 0.02)
Follow up visit 12 weeks (only for SVR12 responders)				
EQ5D-5L Score	292	0.83, 0.19 (0.81, 0.85)	289	0.01, 0.17 (-0.01, 0.03)

Higher scores indicate better health status.
[†] N: number of patients with non-missing score.
[‡] N: number of patients with non-missing baseline score.
End of Treatment visit was at Week 12 for all subjects
Only protocols that have subjects with EQ-5D-5L data are included in the table.

Table 2. Summary of mean and mean change from baseline score for EQ-5D health utility scores over time (PRO FAS) EBR/GZR (12 weeks) in European patients

	European patients			
	N[†]	Mean, SD (95% CI)	N[‡]	Change from Baseline, SD (95% CI)
Baseline				
EQ5D-5L Score	84	0.83, 0.18 (0.79, 0.87)		
Week 4				
EQ5D-5L Score	84	0.83, 0.19 (0.79, 0.87)	81	-0.00, 0.13 (-0.03, 0.03)
End of Treatment				
EQ5D-5L Score	85	0.82, 0.20 (0.77, 0.86)	82	-0.01, 0.16 (-0.05, 0.02)
Follow up visit 12 weeks (only for SVR12 responders)				
EQ5D-5L Score	83	0.85, 0.18 (0.82, 0.89)	80	0.02, 0.15 (-0.02, 0.05)

Higher scores indicate better health status.
[†] N: number of patients with non-missing score.
[‡] N: number of patients with non-missing baseline score.
End of Treatment visit was at Week 12 for all subjects
Only protocols that have subjects with EQ-5D-5L data are included in the table.

- C-EDGE H2H (protocol number: 077):

Table 3. Summary of mean and mean change from baseline score for EQ-5D health utility scores over time (PRO FAS, excluding Hungarian subjects) EBR/GZR (12 weeks) in all patients

	All patients			
	N[†]	Mean, SD (95% CI)	N[‡]	Change from Baseline, SD (95% CI)
Baseline				
EQ5D-5L Score	105	0.88, 0.14 (0.86, 0.91)		
Week 4				
EQ5D-5L Score	104	0.87, 0.17 (0.84, 0.91)	100	-0.02, 0.18 (-0.05, 0.02)
End of Treatment				
EQ5D-5L Score	107	0.90, 0.15 (0.87, 0.93)	103	0.01, 0.12 (-0.01, 0.03)
Follow up visit 12 weeks (only for SVR12 responders)				
EQ5D-5L Score	100	0.91, 0.15 (0.88, 0.93)	96	0.02, 0.14 (-0.01, 0.05)

Higher scores indicate better health status.
[†] N: number of patients with non-missing score.
[‡] N: number of patients with non-missing baseline score.
End of Treatment visit was at Week 12 for all subjects
Only protocols that have subjects with EQ-5D-5L data are included in the table.

Table 4. Summary of mean and mean change from baseline score for EQ-5D health utility scores over time (PRO FAS, excluding Hungarian subjects) EBR/GZR (12 weeks) in European patients

	European patients			
	N[†]	Mean, SD (95% CI)	N[‡]	Change from Baseline, SD (95% CI)
Baseline				
EQ5D-5L Score	83	0.89, 0.13 (0.86, 0.92)		
Week 4				
EQ5D-5L Score	82	0.87, 0.18 (0.83, 0.91)	78	-0.03, 0.18 (-0.07, 0.01)
End of Treatment				
EQ5D-5L Score	87	0.91, 0.14 (0.88, 0.94)	83	0.01, 0.12 (-0.01, 0.04)
Follow up visit 12 weeks (only for SVR12 responders)				
EQ5D-5L Score	83	0.92, 0.13 (0.89, 0.95)	79	0.03, 0.15 (-0.01, 0.06)

Higher scores indicate better health status.
[†] N: number of patients with non-missing score.
[‡] N: number of patients with non-missing baseline score.
End of Treatment visit was at Week 12 for all subjects
Only protocols that have subjects with EQ-5D-5L data are included in the table.

c) SF-36 scores

- C-SURFER (protocol number: 052):

Table 5. Summary Mean and Mean Change from Baseline Score for SF-36v2® Health Utility Scores over Time (PRO FAS) GZR/EBR (12 weeks) in all patients

	All patients			
	N†	Mean, SD (95% CI)	N‡	Change from Baseline, SD (95% CI)
Baseline				
Physical Component Summary	109	42.49, 8.61 (40.85, 44.12)		
Mental Component Summary	109	48.44, 10.26 (46.49, 50.39)		
Week 4				
Physical Component Summary	0	---, --- (---, ---)	0	---, --- (---, ---)
Mental Component Summary	0	---, --- (---, ---)	0	---, --- (---, ---)
End of Treatment				
Physical Component Summary	98	43.88, 8.17 (42.25, 45.52)	98	1.31, 6.72 (-0.04, 2.65)
Mental Component Summary	98	47.33, 10.55 (45.22, 49.44)	98	-1.18, 9.47 (-3.08, 0.71)
Follow up visit 12 weeks (only for SVR12 responders)				
Physical Component Summary	93	43.61, 8.24 (41.91, 45.31)	93	1.30, 7.37 (-0.22, 2.81)
Mental Component Summary	93	48.39, 9.93 (46.35, 50.44)	93	0.23, 9.48 (-1.72, 2.18)

Health Domain Scores, ranging from 0 to 100, with 100 representing the best health status.

PCS and MCS scores were calculated using the individual scores linearly transformed using the population norms to the mean of 50 and a standard deviation of 10.

† N: number of patients with non-missing score.

‡ N: number of patients with non-missing baseline score.

Table 6. Summary Mean and Mean Change from Baseline Score for SF-36v2® Health Utility Scores over Time (PRO FAS) GZR/EBR (12 weeks) in European patients

	European patients			
	N†	Mean, SD (95% CI)	N‡	Change from Baseline, SD (95% CI)
Baseline				
Physical Component Summary	33	43.77, 7.79 (41.01, 46.53)		
Mental Component Summary	33	44.88, 11.44 (40.82, 48.94)		
Week 4				
Physical Component Summary	0	---, --- (---, ---)	0	---, --- (---, ---)
Mental Component Summary	0	---, --- (---, ---)	0	---, --- (---, ---)
End of Treatment				
Physical Component Summary	29	46.70, 7.98 (43.67, 49.74)	29	2.60, 6.58 (0.10, 5.11)
Mental Component Summary	29	45.29, 11.49 (40.92, 49.66)	29	1.39, 10.20 (-2.49, 5.28)
Follow up visit 12 weeks (only for SVR12 responders)				
Physical Component Summary	30	46.00, 8.86 (42.69, 49.31)	30	2.38, 7.27 (-0.33, 5.10)
Mental Component Summary	30	46.16, 11.22 (41.97, 50.35)	30	1.95, 11.48 (-2.34, 6.24)

Health Domain Scores, ranging from 0 to 100, with 100 representing the best health status.

PCS and MCS scores were calculated using the individual scores linearly transformed using the population norms to the mean of 50 and a standard deviation of 10.

† N: number of patients with non-missing score.

‡ N: number of patients with non-missing baseline score.

- C-CO-STAR (protocol number: 062):

Table 7. Summary of Mean and Mean Change from Baseline Score for SF-36v2® Health Utility Scores over Time (PRO FAS) GZR/EBR (12 weeks) in all patients

	All patients			
	N[†]	Mean, SD (95% CI)	N[‡]	Change from Baseline, SD (95% CI)
Baseline				
Physical Component Summary (PCS)	198	48.85, 8.43 (47.67, 50.03)		
Mental Component Summary (MCS)	198	43.65, 11.35 (42.06, 45.24)		
Week 4				
Physical Component Summary (PCS)	177	48.86, 8.81 (47.56, 50.17)	175	-0.09, 6.03 (-0.99, 0.81)
Mental Component Summary (MCS)	177	44.42, 11.15 (42.76, 46.07)	175	0.63, 10.38 (-0.92, 2.18)
End of Treatment				
Physical Component Summary (PCS)	191	48.97, 9.05 (47.67, 50.26)	189	0.05, 7.22 (-0.98, 1.09)
Mental Component Summary (MCS)	191	43.99, 11.78 (42.31, 45.67)	189	0.32, 10.37 (-1.17, 1.80)
Follow up visit 12 weeks (only for SVR12 responders)				
Physical Component Summary (PCS)	165	49.23, 9.47 (47.77, 50.69)	165	0.13, 7.02 (-0.95, 1.20)
Mental Component Summary (MCS)	165	43.97, 11.98 (42.13, 45.81)	165	0.27, 10.59 (-1.36, 1.90)

Health Domain Scores, ranging from 0 to 100, with 100 representing the best health status.

PCS and MCS scores were calculated using the individual scores linearly transformed using the population norms to the mean of 50 and a standard deviation of 10.

[†] N: number of patients with non-missing score.

[‡] N: number of patients with non-missing baseline score.

Table 8. Summary of Mean and Mean Change from Baseline Score for SF-36v2® Health Utility Scores over Time (PRO FAS) GZR/EBR (12 weeks) in European patients

	European patients			
	N[†]	Mean, SD (95% CI)	N[‡]	Change from Baseline, SD (95% CI)
Baseline				
Physical Component Summary (PCS)	53	50.62, 6.95 (48.70, 52.53)		
Mental Component Summary (MCS)	53	45.50, 10.18 (42.69, 48.31)		
Week 4				
Physical Component Summary (PCS)	49	51.73, 6.54 (49.85, 53.61)	49	0.69, 5.59 (-0.92, 2.29)
Mental Component Summary (MCS)	49	44.45, 13.31 (40.62, 48.27)	49	-0.93, 11.97 (-4.36, 2.51)
End of Treatment				
Physical Component Summary (PCS)	49	51.67, 6.86 (49.70, 53.64)	49	1.05, 5.94 (-0.66, 2.75)
Mental Component Summary (MCS)	49	44.77, 13.03 (41.03, 48.51)	49	-0.71, 11.31 (-3.96, 2.54)
Follow up visit 12 weeks (only for SVR12 responders)				
Physical Component Summary (PCS)	41	51.48, 8.45 (48.81, 54.15)	41	0.24, 7.91 (-2.26, 2.74)
Mental Component Summary (MCS)	41	46.66, 10.81 (43.24, 50.07)	41	0.12, 10.34 (-3.14, 3.39)

Health Domain Scores, ranging from 0 to 100, with 100 representing the best health status.

PCS and MCS scores were calculated using the individual scores linearly transformed using the population norms to the mean of 50 and a standard deviation of 10.

[†] N: number of patients with non-missing score.

[‡] N: number of patients with non-missing baseline score.

Section B: Clarification on cost-effectiveness data

Literature searching

B1. In the final scope, the related NICE guidelines are listed as TA 75, TA 106, TA 200, TA 252, TA 253, TA 330, TA 331, TA 363, TA 364 and TA 365. However, in the summary list for identified UK cost-effectiveness studies (table 58, page 159 of the company submission), only TA 252, TA 253, TA 363, TA 364, TA 365 and TA 330 were included. Please explain why TA 75, TA 106, TA 200 and TA 331 were not included.

In order to capture data representative of the current economic environment the searches were limited to the last 10 years (i.e. January 2005 to 20 January 2016). TA75 was published in 2004 and was therefore not captured in the search.

MSD did not report TA106 and TA200 within section 5.1 to avoid duplication as the principal publications (Shepherd et al 2007[17] and Hartwell et al 2011[18]) were identified and included. Shepherd et al 2007[17] was a systematic literature review and cost-effectiveness analysis used to support TA106. Similarly, Hartwell et al 2011[18] was a systematic review and economic evaluation used to support TA200. Both studies are reported in table 58 page 159 of the manufacturer submission.

MSD apologises for missing TA331[19] from the list of identified cost-effectiveness studies. However, the Westerhout et al. 2014[20] abstract relevant to the cost-utility analysis of SMV/PR was identified and extracted in table 58 page 159. Please find in Table 1, Table 2, and Table 3 below a full extraction of TA331:[19]

Table 1. Study characteristics and outcomes reported in the identified cost-effectiveness studies conducted in the UK

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
NICE, 2015 [TA331]	CEA (HTA document)	Type: The model is composed of two phases: treatment phase (0-72 weeks) and post treatment 'Markov' phase (72 weeks-lifetime) Health states: • Treatment phase: Mild HCV (F0-F2), SVR (F0-F2), moderate HCV (F3), SVR (F3), CC (F4), SVR (F4) • Post-treatment phase: DCC, HCC, LT, post LT, liver related death; and death (all-	NHS in England and Wales	• SMV+PEG-IFN+RBV • SMV+SOF • PEG-IFN+RBV • BOC+PEG-IFN+RBV • TVR+PEG-IFN+RBV	TN and TE (prior relapsers, partial and null responders) HCV patients with genotype 1 or 4; TN and TE F3-F4 HCV patients with genotype 1 who were intolerant or ineligible for IFN and in urgent need of treatment	Lifetime	**Discounted QALYs:** TN genotype 1 • PEG-IFN+RBV: 11.653 • SMV+PEG-IFN+RBV: 12.390 • TVR+PEG-IFN+RBV: 12.275 • BOC+PEG-IFN+RBV: 12.242 TE genotype 1 • PEG-IFN+RBV: 10.327 • SMV+PEG-IFN+RBV: 11.258 • TVR+PEG-IFN+RBV: 11.226 • BOC+PEG-IFN+RBV: 11.128 TN genotype 4 • PEG-IFN+RBV: 12.274 • SMV+PEG-IFN+RBV: 13.029 TE genotype 4 • PEG-IFN+RBV:	**Discounted costs:** TN genotype 1 • PEG-IFN+RBV: £26,316 • SMV+PEG-IFN+RBV: £36,778 • TVR+PEG-IFN+RBV: £40,945 • BOC+PEG-IFN+RBV: £38,898 TE genotype 1 • PEG-IFN+RBV: £34,424 • SMV+PEG-IFN+RBV: £43,544 • TVR+PEG-IFN+RBV: £44,502 • BOC+PEG-IFN+RBV: £49,582 TN genotype 4 • PEG-IFN+RBV: £26,836 • SMV+PEG-IFN+RBV: £35,638 TE genotype 4 • PEG-IFN+RBV:	**ICER vs PEG-IFN+RBV:** TN genotype 1 • SMV+PEG-IFN+RBV: £14,206 • TVR+PEG-IFN+RBV: £23,509 • BOC+PEG-IFN+RBV: £21,361 TE genotype 1 • SMV+PEG-IFN+RBV: £9,793 • TVR+PEG-IFN+RBV: £11,209 • BOC+PEG-IFN+RBV: £18,914 **ICER SMV+PEG-IFN+RBV vs comparators:** TN genotype 1 • TVR+PEG-IFN+RBV: Dominant • BOC+PEG-IFN+RBV: Dominant • PEG-IFN+RBV: £14,206 TE genotype 1

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
		cause mortality)					10.732 • SMV+PEG-IFN+RBV: 11.722 **Discounted QALYs for no treatment vs comparators** TN (F3-F4) • No treatment: 9.369 • SMV+SOF: 11.747 • SMV+PEG-IFN+RBV: 11.341 • TVR+PEG-IFN+RBV: 11.001 • BOC+PEG-IFN+RBV: 10.481 TE (F3-F4) • No treatment: 9.239 • SMV+SOF: 11.761 • SMV+PEG-IFN+RBV: 10.307 • TVR+PEG-IFN+RBV: 10.182 • BOC+PEG-IFN+RBV: 10.257 **Discounted QALYs for SMV+SOF vs**	£36,781 • SMV+PEG-IFN+RBV: £45,591 **Discounted costs for no treatment vs comparators** TN (F3-F4) • No treatment: £32,465 • SMV+SOF: £69,081 • SMV+PEG-IFN+RBV: £42,976 • TVR+PEG-IFN+RBV: £48,797 • BOC+PEG-IFN+RBV: £57,486 TE (F3-F4) • No treatment: £33,045 • SMV+SOF: £68,147 • SMV+PEG-IFN+RBV: £52,906 • TVR+PEG-IFN+RBV: £60,075 • BOC+PEG-IFN+RBV: £67,673	• TVR+PEG-IFN+RBV: Dominant • BOC+PEG-IFN+RBV: Dominant • PEG-IFN+RBV: £9,793 **ICER vs PEG-IFN+RBV** TN genotype 4 • SMV+PEG-IFN+RBV: £11,662 TE genotype 4 • SMV+PEG-IFN+RBV: £8,896 **ICER no treatment vs comparators** TN (F3-F4) • SMV+SOF: £15,394 • SMV+PEG-IFN+RBV: £5,329 • TVR+PEG-IFN+RBV: £10,004 • BOC+PEG-IFN+RBV: £22,487 TE (F3-F4) • SMV+SOF: £13,917 • SMV+PEG-IFN+RBV: £18,597 • TVR+PEG-IFN+RBV:

Study name	Study design	Type of model and model health states	Perspective	Intervention/ comparator	Population	Horizon	QALYs	Costs	ICERs (cost/QALY)
							comparators TN (F3-F4) • SMV+SOF: 11.747 • No treatment: 9.369 • SMV+PEG-IFN+RBV: 11.341 • TVR+PEG-IFN+RBV: 11.002 • BOC+PEG-IFN+RBV: 10.478 TE (F3-F4) • SMV+SOF: 11.761 • No treatment: 9.239 • SMV+PEG-IFN+RBV: 10.307 • TVR+PEG-IFN+RBV: 10.182 • BOC+PEG-IFN+RBV: 10.257	**Discounted costs for SMV+SOF vs comparators** TN (F3-F4) • SMV+SOF: £69,170 • No treatment: £32,465 • SMV+PEG-IFN+RBV: £43,051 • TVR+PEG-IFN+RBV: £48,786 • BOC+PEG-IFN+RBV: £57,518 TE (F3-F4) • SMV+SOF: £68,147 • No treatment: £33,045 • SMV+PEG-IFN+RBV: £52,906 • TVR+PEG-IFN+RBV: £60,075 • BOC+PEG-IFN+RBV: £67,673	£28,645 • BOC+PEG-IFN+RBV: £33,997 **ICER SMV+SOF vs comparators** TN (F3-F4) • No treatment: £15,431 • SMV+PEG-IFN+RBV: £64,305 • TVR+PEG-IFN+RBV: £27,365 • BOC+PEG-IFN+RBV: £9,182 TE (F3-F4) • No treatment: £13,917 • SMV+PEG-IFN+RBV: £10,480 • TVR+PEG-IFN+RBV: £5,113 • BOC+PEG-IFN+RBV: £315

Table 2. Study characteristics and outcomes reported in the identified HRQoL and utility studies identified – UK studies

Authors and publication date	Country	Population	Sample size	Intervention/ comparators	Method of elicitation	Model health states	Baseline/population values with confidence intervals	Values by health state with confidence intervals
NICE, 2015 [TA331]	UK	TN and TE (prior relapsers, partial and null responders) HCV patients with GT1 or GT4; TN and TE F3-F4 HCV patients with GT1 who were intolerant or ineligible for IFN and in urgent need of treatment	NR	• SMV+PEG-IFN+RBV • SMV+SOF • PEG-IFN+RBV • BOC+ PEG-IFN+RBV • TVR+PEG-IFN+RBV	• EQ-5D	SVR, mild disease (F0-F2), moderate disease (F3), cirrhosis (F4), HCC, DCC, LT, post-LT, liver related death	• NR	**Utility values for each health state** • Achieve SVR: 0.050 • F0-F2: 0.770 • F3: 0.660 • F4: 0.550 • DCC: 0.450 • HCC: 0.450 • LT: 0.450 • Post-LT: 0.670

Table 3. Characteristics of the cost and resource utilisation studies identified

Author, date	Study description	Population (sample size)	Intervention/ comparator	Sources	Perspective	Resource use	Cost year and discount rate	Cost
Economic evaluations								
NICE, 2015 [TA331]	CEA (HTA document)	TN and TE (prior relapsers, partial and null responders) HCV patients with GT1 or GT4; TN and TE F3-F4 HCV patients with GT1 who were intolerant or ineligible for IFN and in urgent need of treatment (sample size not reported)	• SMV+PEG-IFN+RBV • SMV+SOF • PEG-IFN+RBV • BOC+ PEG-IFN+RBV • TVR+PEG-IFN+RBV	• Drug costs were based on the prices from the British National Formulary (March-September 2014) • Annual health state costs were obtained from several sources including Shepherd et al., 2007 and Hartwell et al., 2011 • Monitoring costs were based on Shepherd et al., 2007 • Adverse event costs were based on Thorlund et al., 2012	NHS in England and Wales	**Associated health care use with adverse events** Anaemia: • Clinic visit (one initial and one follow up) • Erythropoietin treatment (20% of anaemia patients) • Blood transfusion (5% of anaemia patients) Neutropenia • Clinic visit (one initial) Rash • Clinic visit (one initial and one follow up) • Dermatologist visit • Cost of hydrocortisone 1% cream (2 months' supply) Pruritus	• 2012	**Drug acquisition cost per unit** • SMV (150mg): £266.64 • TVR (375mg): £44.44 • BOC (200mg): £ 8.33 • PEG-IFN-2a (180mcg/0.5ml): £124.40 • PEG-IFN-2b (50mcg): £66.46 • PEG-IFN-2b (80mcg): £106.34 • PEG-IFN-2b (100mcg): £132.92 • PEG-IFN-2b (120mcg): £159.51 • PEG-IFN-2b (150mcg): £199.38 • RBV (Copegus [200mg]): £2.20 • RBV (Rebetol [200mg]): £1.91 **Total drug cost per treatment regimen** • SMV (12 wk)+PEG-IFN+RBV (24 wk): £27,220 • SMV (12 wk)+PEG-IFN+RBV

Author, date	Study description	Population (sample size)	Intervention/ comparator	Sources	Perspective	Resource use	Cost year and discount rate	Cost
						• Clinic visit (one initial and one follow up) • Dermatologist visit • Cost of hydroxyzine hydrochloride (25mg capsules, 2 months' supply)		(48 wk): £32,155 • TVR (12 wk)+PEG-IFN+RBV (24 wk): £27,282 • TVR (12 wk)+PEG-IFN+RBV (48 wk): £32,166 • BOC (24 wk)+PEG-IFN+RBV (28 wk): £22,498 • BOC (32 wk)+PEG-IFN+RBV (48 wk): £32,169 • BOC (44 wk)+PEG-IFN+RBV (48 wk): £40,569 • PEG-IFN+RBV (48 wk): £9,769 **Health state costs** • SVR F0-F2: £343 • SVR F3: £343 • SVR F4: £753 • F0-F2: £183 • F3: £949 • F4: £1,506 • DCC: £12,069 • HCC: £10,755 • LT: £48,685 • Post-LT: £1,833

Author, date	Study description	Population (sample size)	Intervention/ comparator	Sources	Perspective	Resource use	Cost year and discount rate	Cost
								Adverse event costs • Anaemia: £889.30 • Neutropenia: £25.58 • Rash: £158.62 • Pruritus: £168.85 **Monitoring costs** First appointment + basic assessment (week 1): • PEG-IFN+RBV: £306 • SMV and TVR: £306 • BOC: £306 Basic assessment (week 2) • PEG-IFN+RBV: £341 • SMV and TVR: £341 • BOC: £341 Week 12 assessment • PEG-IFN+RBV: £711 • SMV and TVR: £907 • BOC: £907 Week 24 assessment • PEG-IFN+RBV: £872 • SMV and TVR: £1,068 • BOC: £1,068 Week 36 assessment

Author, date	Study description	Population (sample size)	Intervention/ comparator	Sources	Perspective	Resource use	Cost year and discount rate	Cost
								• PEG-IFN+RBV: £1,005 • SMV and TVR: £1,200 • BOC: £1,200 Week 48 assessment • PEG-IFN+RBV: £1,166 • SMV and TVR: £1,362 • BOC: £1,362

B2. Please explain why the Scottish Medicine Consortium (SMC) assessment reports for the new treatments in Chronic Hepatitis C had not been identified in Table 58.

MSD does not believe that the limited information presented in the SMC assessment report would allow thorough completion of table 58. For this reason the SMC assessment reports were not identified in table 58.

B3. In Table 58, for the Shepherd et al. 2005 study, the overall ICER estimate is higher than all other subgroup ICER estimates. It is expected that the overall ICER estimate would be within the boundaries of the minimum and maximum ICER estimates from the subgroups. Please check whether this is correct.

The Shepherd et al 2005[21] study reported ICER values for various subgroups: GT1a, GT2/3a, GT2/3b, GT4, GT5, and GT6b, as well as the overall ICER.

Please note that the information solely relevant to the EBR/GZR license was reported in the table. The following results were therefore excluded from table 58:

- GT2/GT3a: ICER = £7,051
- GT2/GT3b: ICER = £37,578

GT2/GT3b ICER (i.e. £37,578) is the upper boundary of the ICER estimates provided. The overall ICER (£12,123) estimate is therefore within the boundaries of the minimum and maximum ICER estimates from the subgroups.

B4. The information presented in table 58 for the Wright et al. 2006 and the Grieve et al. 2006 studies appears the same. Please confirm if these are 2 publications of the same cost-effectiveness analysis.

MSD confirms that both the Wright et al. 2006[22] and the Grieve et al. 2006[23] publications are of the same cost-effectiveness analysis. Grieve et al 2006[23] publication refers to the Wright et al 2006[22] publication.

Population

B5. **Priority request:** The subgroups listed below were included in the NICE final scope as clinically important subgroups for this treatment. Please reconsider whether it would be useful to provide some or all of these analyses (taking into account the anticipated indication in the SmPC and the appraisal committee considerations of previous Hep C topics), otherwise please provide further justification for not providing these analyses.

- People with renal impairment
- People co-infected with HIV
- People with advanced liver disease

- Post-liver transplantation
- People with haemoglobinopathies
- People who are intolerable to and ineligible for IFN treatment

Details of why the above listed subgroups were not considered in the submission are provided in table 1 of the submission (pages 22-23).

In addition, please note that, hepatocellular carcinoma (HCC) and decompensated cirrhosis (DC) were listed as exclusion criteria in our clinical trials thus providing us with no data for the advanced liver disease subgroup.

B6. Treatment experienced patients considered in the economic analyses include patients who are non or partial responders and people with relapsed disease. Chronic hepatitis C treatments may have different effectiveness for each of these subgroups. Please consider exploring the impact of response to previous treatment in subgroup analyses or provide justification why this may not be appropriate.

NICE recommendations for the latest all-oral DAA regimens are based on treatment history but not on the reason of previous treatment failure. Additionally, the licenced dose for these treatments does not depend on treatment history and reason for previous treatment failure. Please note that splitting further the small sample size of treatment experienced patients in each subgroup would limit the robustness of the NMA results

B7. Treatment experienced patients in the economic analyses may include direct acting antiviral (DAA) naïve or DAA experienced patients. Elbasvir/grazoprevir and its comparators may have different effectiveness for DAA naïve and DAA experienced patients.

a. Please provide information on how many of the treatment experienced patients had used DAA before trial inclusion and how many had used non-DAA treatments, for example peginterferon alfa.

All the treatment-experienced patients included from EBR/GZR studies (C-SURFER, C-EDGE TE [24], C-WORTHY [25], and PN077 [16]) had previously received interferon or peginterferon alfa, with or without ribavirin. Of the comparator trials included in the NMA, all treatment-experienced patients had received some combination of interferon or peginterferon alfa, with or without ribavirin, other than:

- 14/52 (27%) patients in ALLY-2 [15] had previously received a protease inhibitor (PI) (n=11; 21%) or sofosbuvir (n=3; 6%). Separate SVRs for those who received a PI and those who didn't are not presented.
- 66/109 (61%) patients in ION-2 [26] had previously received boceprevir (n=16; 15%), telaprevir (n=43; 39%) or another protease inhibitor (n=7; 6%). The SVR for those

who received a PI (62/66; 93.9%) were comparable to those who only received PR (40/43; 93.0%), irrespective of cirrhosis status.

- 17/171 (10%) patients in Mizokami et al., 2015 [8] had previously received a protease inhibitor (either telaprevir, simeprevir, vaniprevir, or valdaprevir). Separate SVRs for those who received a PI and those who didn't are not presented.

- 80/80 (100%) of patients in Pol et al., 2015 [27] had previously received a regimen including an investigational DAA (either vedroprevir/GS-9256, vedroprevir/GS-9256 plus tegobuvir, vedroprevir plus ledipasvir or vedroprevir plus tegobuvir plus ledipasvir).

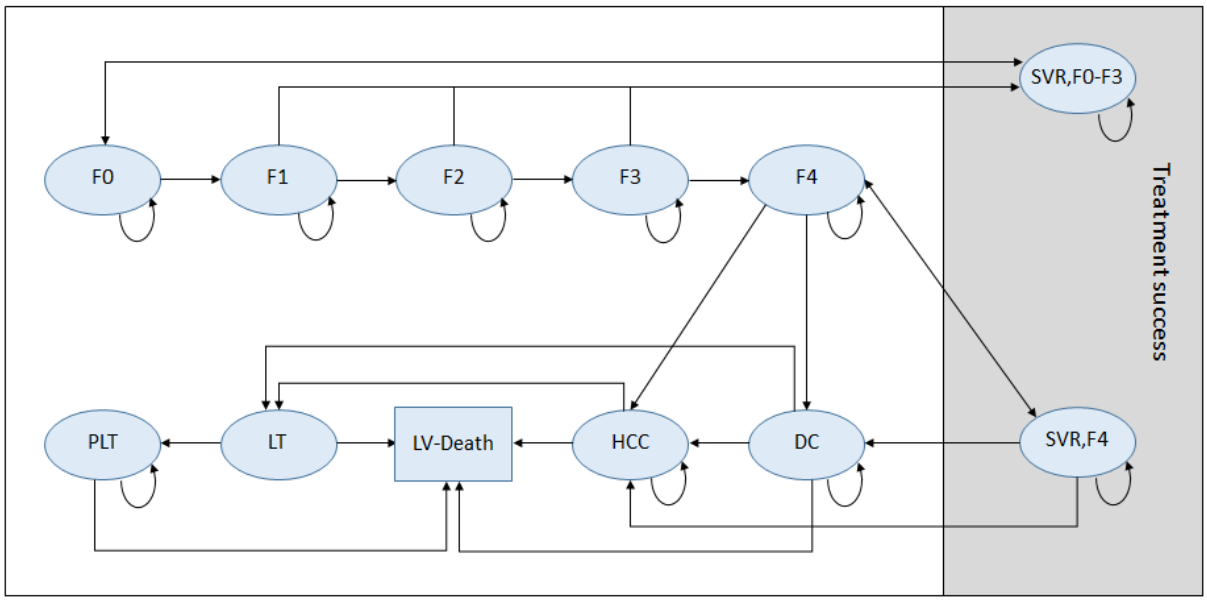
b. Please consider exploring the impact of type of previous treatment (DAA versus non-DAA treatment) in subgroup analyses or provide justification why this may not be appropriate.

Only two trials (ION-2 and Pol et al., 2015)[26,27] of NICE recommended comparators present SVRs for DAA experienced patients. This precluded us from carrying out a sub analysis of this group versus patients previously treated with DAA free regimens.

Model Structure

B8. Figure 16 (page188 of the company submission): There should be no connection possible between F4 and (SVR, F0-F3) states. Please confirm this and provide a corrected version of Figure 16.

MSD apologises for the incorrect model diagram and confirms that no transition from "F4" health state to"SVR,F0-F3" is allowed in the cost-effectiveness model. Please find below the updated diagram:



B9. In the model, patients in SVR F1, SVR F2 and SVR F3 states relapse only to F0 and not to F1, F2 and F3, thus implying that the liver damage caused by chronic hepatitis C is fully reversible. Please justify this assumption.

Patients who achieve SVR can be re-infected. For simplicity the model assumes that non-cirrhotic patients who achieve SVR, grouped in the "SVR,F0-F3" health state, do not get re-infected at F1, F2 or F3 but return to the initial fibrosis state F0. All model assumptions were validated with two clinical experts.

B10. Please justify the modelling assumption that there is no progression to more severe health states while patients are on treatment.

In the economic model patients are assumed to progress only once the treatment has been completed; however all the treatment-related outcomes occur within the first year of the model given the short duration of HCV treatments. This approach is consistent with previous submissions and was validated with two clinical experts.

B11. In the model, it is assumed that all transition probabilities except for sustained virological response, discontinuation and adverse events rates, were identical for all considered chronic hepatitis C treatments.

a. Please justify this assumption that chronic hepatitis C treatment has no effect on disease progression.

The model assumes that the outcomes inherent to the chronic hepatitis C treatments are SVR, discontinuation and AEs rates. The systematic literature did not identify any difference in transition probabilities irrespective of the hepatitis C treatment received; therefore the same transition probabilities were implemented in the model regardless of treatment received. This approach is consistent with previous submissions and was validated with two clinical experts.

b. Also please justify the assumption that the disease progression probabilities are the same between different subgroups (treatment naïve vs treatment experienced; genotypes 1a, 1b and 4).

Although patients with chronic HCV receive different treatments at different durations according to genotype and treatment history; they are not expected to have different transition probabilities according to the different subgroups as no data was identified from the systematic literature review to support this approach. This assumption was validated with two clinical experts.

Intervention/Comparator

B12. **Priority request:** Appendix 1 of the company submission states that the treatment duration for elbasvir/grazoprevir might be increased to 16 weeks with ribavirin at the discretion of physicians. Please provide an estimate of the proportion of patients that would receive this longer duration of treatment with ribavirin.

The SmPC states "should be considered". The SVR rates for 12 weeks are comparable to other agents' available. MSD does not envisage any patient receiving treatment of more than 12 weeks duration given the availability of new DAAs recommended for 12 weeks or less.

B13. **Priority request:** Boceprevir and telaprevir are included as comparators of elbasvir/grazoprevir in the NICE final scope. We note that these comparators have not been included in the company submission on the basis that they are no longer considered current clinical practice. Please reconsider if it is suitable to present analyses using these comparators.

This was discussed during the NICE scoping workshop and validated by the two clinical experts consulted via face to face and telephone interviews. More details are provided on page 20 of the submission.

In addition, MSD has consulted the latest IMS England sales data available (i.e. March 2016) when the clarification questions were received. In March 2016 a total of 32 units of telaprevir and 6 units of boceprevir were sold, respectively equivalent to approximately £60,000 and £15,000 cash sales. These sales are marginal when compared to the all-DAA market where the total number of units sold in March 2016 in England is approximately 32,000 for SOF, LDV/SOF, DCV, 2D/3D combined.[28]

Clinical parameters and variables

B14. **Priority request:** Please describe the methodology used in obtaining the expert opinion for all the clinical assumptions in the model: for example the area of expertise, the reason for only approaching 2 experts, the set of questions posed to the experts during the face-to-face meeting and tele-conference and the individual responses of the two experts.

The two clinical experts were selected on the basis of their expertise in treating HCV in England. The first clinical expert is located in London and the second clinical expert in the north of England. The same questions were asked to both clinical experts, prompted through discussion via a slide deck. The slide deck covered the following points.

After briefly describing the EBR/GZR mechanism of action and the expected license, feedback was gained on the suitability of having boceprevir and telaprevir as comparators

(see question B13). Then, MSD introduced the NMA methodology to overcome the overall lack of comparative clinical trials in HCV to allow efficacy and safety comparisons between agents.

The model health state transition diagram and the different assumptions used in the model (see page 231 and 232 of the submission) formed the main part of the discussion. The two clinical experts validated the assumptions used in the model and highlighted the importance of having consistent assumptions with previous HCV NICE submissions.

B15. In the SVR network meta-analysis results for GT1b patients (table 65, page 196), it can be seen that 100% of the patients achieved SVR with elbasvir/grazoprevir, even though in the discontinuation network meta-analysis results for GT1b patients (Table 66, page 197), it can be seen that some of the GT1b patients on elbasvir/grazoprevir had discontinued treatment. This implies that a patient who discontinues treatment may still achieve SVR.

a. Please justify this assumption.

All SVRs included within the analysis were those based on either the intention to treat (ITT) or modified intention to treat (mITT) populations. The ITT principle requires that all participants of a randomised controlled trial (RCT) that are randomised must be included in the final analysis and analysed according to the treatment group to which they were originally assigned, regardless of the treatment received, withdrawals, loses to follow-up or cross-overs. The use of mITT is on the increase in medical literature[29]; however, there is little consistency in mITT population definitions[30]. The definition of the mITT population (also called the full analysis set)[31] used in clinical trials included within the SLR was all patients who underwent randomisation and received at least one dose of the study drug. Examples include C-EDGE TN[1] (3 patients discontinued treatment due to drug related adverse events, 2 of which went on to achieve an SVR), ION-1[6] (10 patients in the study discontinued treatment but were subsequently found to have achieved SVR, where the shortest duration of treatment was 8 weeks) and SAPPHIRE-I[32] (3 patients in the immediate treatment arm discontinued treatment due to adverse events, 2 did not achieve an SVR at post treatment week 12 but 1 did after discontinuing treatment at week 11).

b. Please also explain if all network meta-analyses (SVR, discontinuation, AEs) use the same ad-hoc analysis data type (e.g. Intention to treat, discontinuation= treatment failure).

Please see the response above, question B15A.

B16. Tables 65 to 67, pages 196 to 198 of the company submission: Please provide confidence intervals in addition to the standard errors for the network meta-analyses results (relative risks of adverse events, discontinuation and SVR rates) for the treatments listed in the tables.

Please note that these can be found in Tables 38-49 in section 4.10.14-16 of the main submission. Alternatively, all the NMA results are reported in Appendix 10 of the appendices document MSD UK_IDF 842 Appendices 1-23. Tables 38-49 of the main submission have been replicated below.

Table 1. NMA SVR results for therapies for GT1a TN NC patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	481 (6)	96.72 (95.04, 98.40)	--	--
PR 1-48	649 (4)	49.96 (46.16, 53.77)	**1.90 (1.76, 2.06)**	**1.86 (1.70, 2.03)**
SMV+PR 1-12, PR 13-24 or PR 13-48	537 (3)	81.76 (78.50, 85.03)	**1.16 (1.11, 1.21)**	**1.20 (1.09, 1.42)**
SOF+PR 1-12	31 (2)	97.61 (90.34, 100.00)	1.01 (0.92, 1.11)	1.05 (0.95, 1.46)
LDV/SOF 1-8	171 (1)	92.98 (89.15, 96.81)	1.02 (0.97, 1.07)	1.01 (0.95, 1.16)
OMB+PAR/r+DAS+R 1-12	491 (3)	96.10 (94.39, 97.81)	0.99 (0.96, 1.02)	0.98 (0.93, 1.03)
DCV+SOF 1-12	60 (1)	96.67 (92.12, 100.00)	0.98 (0.93, 1.03)	0.98 (0.93, 1.13)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

NMA SVR results for therapies for GT1 TN C patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	104 (5)	96.23 (92.15, 100.00)		
PR 1-48	32 (2)	34.00 (17.68, 50.31)	**2.77 (1.71, 4.48)**	**2.68 (2.00, 3.80)**
SMV+PR 1-12, PR 13-24 or PR 13-48	48 (2)	60.51 (46.72, 74.31)	**1.58 (1.25, 1.99)**	**1.50 (1.06, 3.90)**
SOF+PR 1-12	10 (1)	80.00 (55.21, 100.00)	1.19 (0.87, 1.63)	1.18 (0.96, 7.19)
LDV/SOF 1-12	59 (4)	97.15 (91.65, 100.00)	0.99 (0.92, 1.05)	1.00 (0.92, 1.11)
OMB+PAR/r+DAS+R 1-24	56 (1)	92.86 (86.11, 99.60)	1.03 (0.94, 1.12)	1.04 (0.94, 1.78)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

NMA SVR results for therapies for GT1a TE NC patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	62 (4)	92.65 (85.59, 99.72)		--
PR 1-48	113 (1)	38.05 (29.10, 47.00)	**2.42 (1.89, 3.09)**	**2.28 (1.68, 2.95)**
SMV+PR 1-12, PR 13-24 or PR 13-48	211 (1)	80.09 (74.71, 85.48)	**1.15 (1.04, 1.27)**	1.13 (0.87, 2.55)
SOF+PR 1-12	69 (2)	79.93 (70.44, 89.42)	**1.15 (1.00, 1.33)**	1.12 (0.86, 2.17)
LDV/SOF 1-12	254 (4)	98.26 (96.45, 100.00)	0.96 (0.89, 1.03)	0.96 (0.76, 1.04)
OMB+PAR/r+DAS+R 1-12	192 (2)	96.58 (93.88, 99.28)	0.95 (0.88, 1.03)	0.96 (0.76, 1.07)
DCV+SOF 1-12	20 (1)	100.00 (29.10, 100.00)	**0.92 (0.86, 0.99)**	0.97 (0.77, 1.37)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

NMA SVR results for therapies for GT1a TE C patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	34 (3)	91.14 (81.32, 100.00)		
PR 1-48	19 (1)	26.32 (6.52, 46.12)	**3.46 (1.62, 7.41)**	**4.03 (2.23, 6.79)**
SMV+PR 1-12, PR 13-24 or PR 13-48	39 (1)	74.36 (60.65, 88.06)	1.23 (0.99, 1.52)	1.30 (0.79, 17.76)
SOF+PR 1-12	14 (1)	71.43 (47.76, 95.09)	1.28 (0.90, 1.81)	1.33 (0.77, 26.22)
LDV/SOF 1-12	77 (4)	98.48 (94.64, 100.00)	0.99 (0.87, 1.12)	0.99 (0.63, 1.22)
OMB+PAR/r+DAS +R 1-24	65 (1)	95.38 (90.28, 100.00)	0.96 (0.85, 1.08)	1.00 (0.66, 3.14)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

NMA SVR results for therapies for GT1b TN NC

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	272 (6)	98.27 (96.59, 99.94)		
PR 1-48	649 (4)	49.96 (46.16, 53.77)	**1.95 (1.80, 2.11)**	**1.92 (1.67, 2.25)**
SMV+PR 1-12, PR 13-24 or PR 13-48	537 (3)	81.76 (78.50, 85.03)	**1.19 (1.14, 1.24)**	**1.24 (1.11, 1.53)**
SOF+PR 1-12	64 (2)	96.76 (92.29, 100.00)	1.00 (0.95, 1.05)	1.00 (0.97, 1.09)
LDV/SOF 1-8	43 (1)	97.67 (93.17, 100.00)	0.99 (0.94, 1.05)	1.02 (0.97, 1.27)
OMB+PAR/r+DAS 1-12	292 (2)	98.84 (97.62, 100.00)	0.98 (0.96, 1.01)	0.99 (0.96, 1.02)
DCV+SOF 1-12	12 (1)	100.00 (46.16, 100.00)	**0.97 (0.95, 0.99)**	1.00 (0.97, 1.50)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response

NMA SVR results for therapies for GT1b TN C

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	78 (6)	100.00 (17.68, 100.00)		
PR 1-48	32 (2)	34.00 (17.68, 50.31)	**2.86 (1.79, 4.58)**	**2.89 (2.11, 4.25)**
SMV+PR 1-12, PR 13-24 or PR 13-48	48 (2)	60.51 (46.72, 74.31)	**1.65 (1.31, 2.07)**	**1.58 (1.06, 5.45)**
SOF+PR 1-12	12 (1)	91.67 (76.03, 100.00)	1.09 (0.92, 1.29)	1.09 (0.99, 4.37)
LDV/SOF 1-12	59 (4)	97.15 (91.65, 100.00)	1.03 (0.99, 1.09)	1.01 (0.96, 1.16)
OMB+PAR/r+DAS +R 1-12	22 (1)	100.00 (96.83, 100.00)	1.00 (0.95, 1.05)	1.01 (0.97, 1.62)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

NMA SVR results for therapies for GT1b, TE NC patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	63 (4)	99.12 (95.12, 100.00)		
PR 1-48	113 (1)	38.05 (29.10, 47.00)	**2.54 (2.00, 3.23)**	**2.58 (2.04, 3.32)**
SMV+PR 1-12, PR 13-24 or PR 13-48	211 (1)	80.09 (74.71, 85.48)	**1.21 (1.12, 1.31)**	1.22 (0.98, 5.25)
SOF+PR 1-12	36 (2)	84.68 (73.04, 96.32)	1.16 (1.00, 1.35)	1.16 (0.97, 3.37)
LDV/SOF 1-12	254 (4)	98.26 (96.45, 100.00)	1.01 (0.96, 1.06)	1.00 (0.89, 1.09)
OMB+PAR/r+DAS 1-12	91 (1)	100.00 (29.10, 100.00)	0.97 (0.93, 1.01)	0.99 (0.89, 1.21)
DCV+SOF 1-12	8 (1)	100.00 (95.12, 100.00)	0.97 (0.93, 1.01)	1.00 (0.90, 1.79)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response

NMA SVR results for therapies for GT1b TN C patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	16 (3)	100.00 (6.52, 100.00)		
PR 1-48	19 (1)	26.32 (6.52, 46.12)	**3.53 (1.74, 7.13)**	**3.58 (2.10, 6.13)**
SMV+PR 1-12, PR 13-24 or PR 13-48	39 (1)	74.36 (60.65, 88.06)	**1.34 (1.12, 1.60)**	1.27 (0.84, 17.95)
SOF+PR 1-12	8 (1)	50.00 (15.35, 84.65)	**1.92 (1.00, 3.69)**	1.60 (0.93, 55.93)
LDV/SOF 1-12	77 (4)	98.48 (94.64, 100.00)	**1.08 (1.02, 1.16)**	1.00 (0.70, 1.20)
OMB+PAR/r+DAS +R 1-12	46 (1)	97.83 (93.61, 100.00)	1.02 (0.98, 1.07)	1.02 (0.75, 4.08)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

NMA SVR results for therapies for GT4 TN NC patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	54 (4)	96.97 (91.54, 100.00)		
PR 1-48	38 (1)	39.47 (23.93, 55.01)	**2.35 (1.57, 3.50)**	**2.36 (1.57, 3.65)**
SMV+PR 1-12, PR 13-24 or PR 13-48	32 (1)	84.38 (71.79, 96.96)	1.10 (0.93, 1.30)	1.09 (0.84, 29.18)
OMB+PAR/r+R 1-12	42 (1)	100.00 (23.93, 100.00)	**0.93 (0.86, 1.00)**	1.00 (0.79, 4.62)
DCV+PR 1-24 or DCV+PR 1-24, PR 25-48	69 (1)	71.01 (60.31, 81.72)	**1.30 (1.10, 1.54)**	1.35 (0.90, 59.42)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

NMA SVR results for therapies for GT 4 TN C patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	6 (2)	100.00 (0.00, 100.00)		
PR 1-48	4 (1)	25.00 (0.00, 67.43)	3.14 (0.80, 12.34)	**5.26 (2.11, 9.85)**
SMV+PR 1-12, PR 13-24 or PR 13-48	3 (1)	66.67 (13.32, 100.00)	1.43 (0.71, 2.88)	1.23 (0.55, 82.71)
SOF+PR 1-12	74 (3)	83.77 (75.45, 92.09)	**1.21 (1.09, 1.34)**	1.11 (0.50, 2.17)
LDV/SOF 1-12	59 (4)	97.15 (91.65, 100.00)	1.03 (0.99, 1.08)	1.00 (0.44, 1.21)
OMB+PAR/r+R 1-24	47 (1)	97.87 (93.75, 100.00)	1.02 (0.98, 1.06)	1.02 (0.49, 3.23)
DCV+PR 1-24 or DCV+PR 1-24, PR 25-48	9 (1)	77.78 (50.62, 100.00)	1.26 (0.91, 1.75)	1.25 (0.57, 18.75)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

NMA SVR results for therapies for GT4 TE NC patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	5 (2)	100.00 (29.10, 100.00)		
PR 1-48	113 (1)	38.05 (29.10, 47.00)	**2.59 (2.06, 3.27)**	2.59 (0.91, 3.94)
SMV+PR 1-12, PR 13-24 or PR 13-48	44 (1)	63.64 (49.42, 77.85)	**1.55 (1.25, 1.93)**	1.43 (0.55, 26.21)
LDV/SOF 1-12	254 (4)	98.26 (96.45, 100.00)	**1.04 (1.02, 1.07)**	1.00 (0.38, 1.14)
OMB+PAR/r+R 1-12	49 (1)	100.00 (74.30, 100.00)	1.00 (0.88, 1.13)	1.00 (0.39, 1.87)
DCV+PR 1-24 or DCV+PR 1-24, PR 25-48	69 (1)	71.01 (60.31, 81.72)	**1.40 (1.21, 1.62)**	1.34 (0.55, 22.38)
DCV+SOF 1-12	28 (1)	100.00 (49.42, 100.00)	1.00 (0.85, 1.18)	1.00 (0.40, 2.11)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviations.** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response.

NMA SVR results for therapies for GT4 TE C patients

Comparison	Number of patients (arms)	Pooled SVR *% (95% confidence interval)*	Naïve comparison *Relative risk (95% confidence interval)*	Network meta-analysis (random effects) *Relative risk (95% credible interval)*
EBR/GZR 1-12 vs.	6 (1)	66.67 (28.95, 100.00)		
PR 1-48	19 (1)	26.32 (6.52, 46.12)	2.53 (0.99, 6.49)	2.47 (0.06, 5.67)
SMV+PR 1-12, PR 13-24 or PR 13-48	28 (1)	46.43 (27.96, 64.90)	1.44 (0.72, 2.87)	1.45 (0.04, 30.13)
SOF+PR 1-12	22 (2)	64.61 (45.07, 84.15)	1.05 (0.55, 2.00)	0.96 (0.03, 6.40)
LDV/SOF 1-12	77 (4)	98.48 (94.64, 100.00)	0.72 (0.41, 1.28)	0.65 (0.02, 1.09)
OMB+PAR/r+R 1-24	52 (1)	96.15 (90.93, 100.00)	0.69 (0.39, 1.22)	0.68 (0.02, 2.03)
DCV+PR 1-24 or DCV+PR 1-24, PR 25-48	9 (1)	77.78 (50.62, 100.00)	0.86 (0.44, 1.67)	0.70 (0.02, 3.10)

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00). **Abbreviation:** DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, peginterferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response

Utilities

B17. **Priority request:** Utilities derived from the clinical trials (Table 70 and Table 71) are comparable to the quality of life values from the general population (Table 74). Furthermore, the utilities found in the Wright study, which are used in the base case analyses (Table 75), are substantially lower.

a. Please provide an explanation for this difference.

MSD believes it is coincidence that the general population and those included in the EBR/GZR clinical trials are broadly similar at age 45-54. It should be noted that patients included in EBR/GZR clinical trials were non-UK participants.

Therefore, underlying factors/differences in populations i.e. geographic regions (non-UK vs. UK patients) and disease background (HCV patients vs. general population) could have impacted these utility values.

b. Please provide the rationale for the choice of the utility data from Wright et al (2006), apart from the fact that it was used in previous health technology appraisals.

MSD believes that as the Wright et al. 2006[22] utility values were derived from UK patients, these more accurately reflect the impact of the disease on the HRQoL of UK patients.

c. Please clarify why data from 2006 can be considered to be representative for the current patient population in the UK.

The HRQoL studies identified by the SLR did not reveal any differences in the HRQOL of the UK patients over the last 10 years. However, as described in section 5.4.6, on treatment-utility decrements were described for EBR/GZR and comparators of interest, all of which have become available since 2012.

B18. **Priority request:** The 3L crosswalk algorithm (page 204) was developed as an interim method to value EQ-5D-5L health states, in the absence of a UK value set. The value set for the EQ-5D-5Lis now available and published and it was shown that there is a relevant and significant difference in the range of the utility scale attainable between the 3L and the 5L. Therefore, please provide the updated model results using the utility estimates based on the EQ-5D-5L tariff as developed by Devlin et al. (2016), rather than the 3L crosswalk algorithm.

Within the manufacturer submission MSD presented utility estimates as change from baseline using absolute values i.e. utility decrements and increments. MSD anticipates that if a different value set were to be used, i.e. EQ-5D-5L tariff, the mean EQ-5D values will be affected equally, thus not impacting the absolute difference of the values.

B19. **Priority request:** Page 203 of the company submission: The derivation of the utility decrements from adverse events was described as follows: "*The impact of any AEs on patients' HRQoL was captured in EQ-5D data as part of the change from baseline. To account for any improvement in HRQoL that may have occurred as a result of treatment response, the utility decrement related to AEs has been derived as the difference between baseline and the mean utility values at week 4 and end-of-treatment. An overall utility decrement of 0% was reported across all patients in the EBR/GZR trials.*"

- It is not clear how these values are generated. Please provide further clarification of the method used to derive the utility decrements due to adverse events and provide a justification for this approach.

MSD estimated the mean EQ-5D utility values at baseline and while on treatment, i.e. week 4 and week 12. Consistent with the methodology implemented in previous submissions, any impact in terms of AEs is captured as the difference between baseline and while on treatment. However, as SHTAC ERG group suggested, it is possible that the EQ-5D scores captured at the end of treatment may be affected by positive treatment response. Thus, to account for this effect, MSD estimated the mean EQ-5D value of week 4 and end-of-treatment (week 12), and applied the change from baseline as utility decrement.

B21. Page 244 of the company submission: Please clarify the rationale for using age-dependent utility decrements in a linear way, given that the EQ-5D data is based on questionnaires filled by patients representing a wide range of ages, thus already incorporating the impact of age. Please clarify how double counting of the impact of age is avoided in the submission.

MSD implemented the same age-dependent linear utility decrements methodology employed in previous UK cost-effectiveness studies.[33] These were based on the UK general population utility data published in the Kind et al study.[34]

The age-dependent utility decrements are required to be applied to the baseline health-state utilities to account for the general decline of HRQoL over time. This is particularly important as EBR/GZR and the majority of the comparators have very high SVR rates which means most patients would be in the "SVR,F0-F4" health state following treatment and remain in this health state until death. The application of age-dependent utility decrements represent more realistically the change in HRQoL of the patients over time, as otherwise the patients would have the same utility values until death. Therefore, MSD believes there is no double counting of the impact of age when the age-dependent utility decrements were applied.

Costs

B22. Page 226 of the company submission: Costs for outpatient visits, inpatient care, tests and investigations have been included in the model. Please clarify whether this captures all relevant resource use. For example, clarify whether patients use allied health care, GP visits, other medication or home care.

As per table 77 page 226 of the manufacturer submission, the on-treatment monitoring costs for the different regimens were derived from the LDV/SOF submission. The unit costs are presented in the LDV/SOF manufacturer's submission appendix 15. MSD believes these costs capture all relevant unit costs and resource use.

Results

B23. Please comment on the observed differences in clinical and economic outcomes between elbasvir/grazoprevir and other DAAs, as it was stated that there was no significant difference between DAAs and elbasvir/grazoprevir in the clinical effectiveness section of the company submission.

The NMA revealed no significant differences between EBR/GZR and the other all-DAA regimens (LDV/SOF, 2D/3D, and DCV+SOF) in any of the subgroups that were investigated. The QALY results observed in the cost-effectiveness analysis follow the same pattern as the SVR results of the NMA, with EBR/GZR and the latest all-oral DAA regimens accruing similar QALYs; this is higher than those regimens containing IFN.

As highlighted in the submission, the economic results were based on EBR/GZR and comparators list prices, due to the lack of publicly available information on CMU prices. Thus, the economic results should be considered indicative and not reflective of the costs attributed to HCV treatment technologies.

B24. Section 5.8.3 of the company submission: Please provide further interpretation of the scenario analyses to accompany the tables of results and figures provided. For example, please explain what drives the presented results, that is, through which mechanisms certain input changes influence the outcomes.

Overall, any difference in the results presented in the scenario analysis section of the submission can be attributed to the structural changes or the alternative parameter sources assessed in each scenario.

Model Validation

B25. Appendix 23 of the company submission: It is stated that that health economics expert validation and computerized model validation had been conducted. No details of the expert validation were provided. Please provide the details of this validation exercise, and also provide a completed version of the checklist in Appendix 23.

A health economist, expert in HCV, was consulted to validate the treatment groups, comparators, structure, inputs and assumptions implemented in the model. In addition, the base case and scenario analyses were also discussed.

The checklist followed for the internal validation of the model presented in appendix 23 is complete and every single item of this checklist was used to validate the model.

B26. Please consider conducting additional validation of the model (such as cross-validation, validation against external data, validation against internal data, clinical expert face validation).

MSD believes all necessary validation of the model has been conducted and does not believe that further validation would provide additional value to the model.

Section C: Textual clarifications and additional points

C1. Table 1, page 20 of the company submission: Please explain what the term “OTVF” stands for.

OTVF (on-treatment virologic failure) was mentioned in the original SmPC discussed during the decision problem meeting. However, the draft SmPC presented supporting this submission does no longer contain the OTVF terminology.

C2. Page 39 of the company submission. Please provide a reference for the following statement: "*If left untreated a patients' deteriorating QoL could also have a negative impact on carers."*

Several studies on how carers would be impacted by patient's QoL deterioration have been published. Whether these publications are disease specific (e.g. cancer, Alzheimer's disease, Parkinson's disease) or not, they highlight the carers' QoL is negatively affected as they care for incapacitated individuals.[35-37]

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Dear Kate (ERG),

Please note that MSD have uploaded three documents via NICE.docs:

- Excel doc. NMA format SVR data
- Excel doc. NMA format safety data
- Word doc. SVR/ Safety data for deferred treatment arms (C-SRUFER, C-EDGE CO-STAR, C-EDGE TN)

When the ERG refers to the placebo groups for questions A5, A7a, and A7b please note:

- This only applies to EBR/GZR trials C-SURFER, C-EDGE CO-STAR, and C-EDGE TN. None of the other EBR/GZR trials had a control/ placebo (deferred) treatment group.
- The reason these data had not previously been taken into consideration, was that these patients were not included in the primary hypothesis, and this was reflected in the power calculations of each of the respective studies.
- In addition, it is not possible for there to be an SVR12 following treatment with placebo, as these patients underwent only a 4 week washout period and then received GZR/EBR.
- It is presumed that patients treated with placebo would not have self-cleared their HCV infection, and for that reason received active therapy following washout. This same assumption is used in the health economic model.
- Please note that the placebo group in each of the trials listed above was used to facilitate blinding and the assessment of safety and tolerability in the absence of an active comparator.

Yours sincerely,

[redacted]

On behalf MSD UK

Sustained viral responses from deferred treatment arms in MSD trials

Trial	Genotype	Treatment History	Cirrhosis Status	Subjects in population	Number with SVR12 (%)
C-SURFER	Genotype 1a	Naïve	No cirrhosis	35	33 (94.3)
C-SURFER	Genotype 1a	Naïve	Cirrhosis	3	3 (100.0)
C-SURFER	Genotype 1a	Experienced	No cirrhosis	11	11 (100.0)
C-SURFER	Genotype 1a	Experienced	Cirrhosis	-	-
C-SURFER	Genotype 1b	Naïve	No cirrhosis	39	39 (100.00)
C-SURFER	Genotype 1b	Naïve	Cirrhosis	1	1 (100.00)
C-SURFER	Genotype 1b	Experienced	No cirrhosis	6	6 (100.00)
C-SURFER	Genotype 1b	Experienced	Cirrhosis	2	2 (100.00)
C-EDGE TN	Genotype 1a	Naïve	No cirrhosis	42	37 (88.1)
C-EDGE TN	Genotype 1a	Naïve	Cirrhosis	10	9 (90.0)
C-EDGE TN	Genotype 1b	Naïve	No cirrhosis	32	31 (96.9)
C-EDGE TN	Genotype 1b	Naïve	Cirrhosis	8	8 (100.0)
C-EDGE CO-STAR	Genotype 1a	Naïve	No cirrhosis	52	47 (90.4)
C-EDGE CO-STAR	Genotype 1a	Naïve	Cirrhosis	16	14 (87.5)
C-EDGE CO-STAR	Genotype 1b	Naïve	No cirrhosis	11	10 (90.9)
C-EDGE CO-STAR	Genotype 1b	Naïve	Cirrhosis	3	3 (100.0)

Safety outcomes from deferred treatment arm in MSD trials

Trial		Genotype 1, no cirrhosis		Genotype 1, cirrhosis	
		n	%	n	%
C-SURFER	Subjects in population	94	100.0%	7	100.0%
	Adverse events	54	57.4%	6	85.7%
	Discontinuations due to adverse events	2	2.1%	1	14.3%
	Anemia	2	2.1%	0	0.0%
	Pruritus	1	1.1%	0	0.0%
	Nausea	9	9.6%	1	14.3%
	Neutropenia	0	0.0%	0	0.0%
	Rash	1	1.1%	1	14.3%
	Thrombocytopenia	0	0.0%	0	0.0%

C-EDGE TN	Subjects in population	74	100.0%	18	100.0%
	Adverse events	53	71.6%	10	55.6%
	Discontinuations due to adverse events	0	0.0%	0	0.0%
	Anemia	0	0.0%	0	0.0%
	Nausea	1	1.4%	0	0.0%
	Neutropenia	7	9.5%	0	0.0%
	Pruritus	0	0.0%	0	0.0%
	Rash	2	2.7%	0	0.0%
	Thrombocytopenia	0	0.0%	0	0.0%
C-EDGE CO-STAR	Subjects in population	66	100.0%	19	100.0%
	Adverse events	45	68.2%	16	84.2%
	Discontinuations due to adverse events	0	0.0%	0	0.0%
	Anemia	0	0.0%	0	0.0%
	Nausea	3	4.5%	0	0.0%
	Neutropenia	4	6.1%	3	15.8%
	Pruritus	0	0.0%	0	0.0%
	Rash	1	1.5%	0	0.0%
	Thrombocytopenia	0	0.0%	0	0.0%

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: The Hepatitis C Trust

Your position in the organisation: [redacted]

Brief description of the organisation: The national patient charity for people living with or affected by hepatitis C funded by grant-making trusts, individual donations, some government grants and grants from industry. We have 4,500 members of our patient association.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

This varies. Some people experience few if any symptoms, while others can be so debilitated that they cannot work and find much of their social/emotional/sexual life significantly impaired (by for example chronic fatigue, mood swings and sexual dysfunction). Equally some people encounter stigma (because of the association with drug use usually) and even discrimination, including loss of job. People who were infected through the NHS often feel extremely angry and bitter because they feel the government has never accepted responsibility or adequately compensated them. People living with hepatitis C are currently experiencing significant uncertainty about when they will have access to interferon-free therapy and hence a cure because NHS England has introduced a cap on the number to be tteated in 2016/17 in apparent direct contravention of NICE technology guidance.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

A cure. For people with significant symptoms (and many more people than is commonly thought do experience symptoms – but they don't realise it until after a cure and disappearance of those symptoms) it can mean a whole new life

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

4. Through our helpline, our support groups and other support services we are in touch with patients daily. Their experience of current NHS care is hugely variable. Many are receiving highly effective interferon-free therapy, are being cured and are generally delighted with the service and with being hepatitis C-free. However, many are also exasperated with the new Operational Delivery Networks (ODNs) through which all secondary hepatitis C care has been delivered since August 2015. These took some months to start functioning properly and there was great confusion about patients' eligibility for treatment and the timing of that treatment. This still persists because NHS England has introduced 'run rates' which strictly limit how many patients can be treated each month by each ODN, irrespective of capacity. The new treatments with their very high efficacy, minor side-effects and short duration are extremely acceptable. They are much preferred to those regimens that still contain interferon. What

do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

A cure (SVR) with consequent improvement in life expectancy and quality of physical, emotional, social, employment and sexual life

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

There are currently many treatments or combinations available. The main advantage is over those containing interferon, which is generally toxic and can have long-term complications.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None known

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Lack of access for some

Waiting times because of NHSE's rationing

Continued use of interferon for some genotypes

Please list any concerns patients or carers have about the treatment being appraised.

None known

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None known

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Trials with this treatment have been conducted both in people who inject drugs and in people with renal problems with very good results, suggesting these groups may particularly benefit

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

None known

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☑ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Not currently in use

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes. SVR is the key outcome, equating to cure. We are not aware of any limitations.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not currently in use

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☑ Yes ☐ No

If yes, please provide references to the relevant studies.

Max Hopwood 'Recovery from hepatitis C treatments' University of New South Wales 2009

http://www.hepctrust.org.uk/Resources/HepC%20New/Hep%20C%20Resources/Reports/Recovery_from_hepatitis_C_treatments.pdf

The Hepatitis C Trust 'Post-treatment survey report' 2010

http://www.hepctrust.org.uk/Resources/HepC%20New/Hep%20C%20Resources/Reports/Post%20Treatment%20Survey%20Report%202010.pdf

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

N/AN/A

9. Other issues

Do you consider the treatment to be innovative?

☑ Yes No

If yes, please explain what makes it significantly different from other treatments for the condition.

It has been shown to be very effective in two specific groups – those with renal disease and people who inject drugs

Are there any other issues that you would like the Appraisal Committee to consider?

Current drug prices for the treatment of hepatitis C are high given the large numbers requiring treatment. More competition will likely drive down prices

10. Key messages

In no more than 5 bullet points, please summarise the key messages of

your submission.

- This treatment could finally banish use of interferon for all genotypes
- It appears very suitable for those with renal disease
- It appears to be very effective in people who use drugs
- New drugs in this field will help to drive down prices

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: BASL / BVHG

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? **No**
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: Nil

Many thanks for requesting feedback and comments on the scope for Elbasvir/Grazoprevir technology appraisal for HCV treatment.

BASL & the British Viral Hepatitis Group welcome NICE's decision to review this very promising regimen.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

We have only minor comments on the present document and plans:

- *In terms of 'Comparators' we would like to highlight that neither Boceprevir nor Telaprevir are utilized clinically in patients (they have been superseded). Therefore the comparison with these technologies is not clinically useful, however we appreciate it may be scientifically required for the full assessment of this technology.*
- *NICE are also performing a review of Sofosbuvir/Velpatasvir for treatment in HCV, and marketing authorization is expected in a similar timecourse to the present technology being assessed. We would welcome the possibility of therefore utilizing Sofosbuvir/Velpatasvir as a comparator also, but appreciate that this may not be permissible.*
- *On a minor point Sofosbuvir/Ledipasvir can be given 'with or without Ribavirin' – as stated with the other comparators*
- *Under 'Outcomes' the time-point for SVR should be stated – this is usually SVR12 (at 12 weeks after completion of treatment).*
- *Under 'Other Considerations' it will be important to assess comparative efficacies with existing technologies for sub-genotypes as well as genotypes – especially G1a and G1b; and to consider patients with decompensated cirrhosis as a specific subgroup.*

Many thanks again for allowing us to respond and we look forward to the progress of this important appraisal.

What is the expected place of the technology in current practice?

It would be expected that this technology will be used primarily for those with chronic hepatitis C genotypes 1 and 4. Currently these are usually treated with either Sofosbuvir/Ledipasvir (+/- Ribavirin), Ombitasvir/Paritaprevir/Ritonavir +/- Dasubuvir +/- Ribavirin, or Sofosbuvir + Peg-interferon + Ribavirin within the NHS. The choices between these therapies are based mostly on commissioning guidance and cost, though drug-interactions and tolerability (for interferon) are also factors. There are no significant differences in opinion amongst clinicians.
This technology has demonstrated excellent efficacy and tolerability in these genotypes and would be a very welcome addition to the options. It may become a front-runner for use in these genotypes, but also has a wealth of good data (in comparison to its competitors) for use in those with significant renal impairment. There do not appear to be any significant disadvantages.

This, and similar technologies, are utilised under the supervision of specialist services (in England based on operation delivery networks (ODNs)). The therapies may be provided, and the patients reviewed at, varying settings including prisons, primary care, drug services etc, but under the umbrella of the ODN.

This technology is not yet available for use in the UK, and is not presently included in guidelines utilised in the UK.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

The advantages and disadvantages of the technology

It is likely that this technology would be clinically interchangeable with Sofosbuvir/Ledipasvir and Ombitasvir/Paritaprevir/Ritonavir +/- Dasabuvir. There are no informative direct head-to-head comparisons but the data available from the Phase 3 studies seem comparable. The decisions on use in the UK may well be made predominately therefore on cost, though there is a specific niche in those with significant renal impairment and/or on dialysis.
In the clinical studies this technology was easy to utilise, with very few adverse events – again comparable with the other current all-oral regimens. There are therefore no direct practical implications except for any possible recommendation for pre-treatment resistance testing (licensing in the US recommends such resistance testing but that in Canada does not, and EU licensing is awaited).

This technology has not yet been utilised outside of clinical studies in the UK. However early data is emerging from the US and elsewhere, from real-world cohorts. It is not expected that clinical practice and results will differ significantly from the study data, as they have not done for the current comparator technologies.
The clinical trial programme included UK sites and is translatable to the UK population and patients.

SVR12 is the recognised primary endpoint both in clinical studies and clinical practice, and was the endpoint utilised in the study programme for this technology.

As described above the side effect profile is very mild, with no consequent significant impact upon the therapy, patient or outcomes.

Any additional sources of evidence

The evidence will be that from the clinical trial programme, which I would assume has been fully provided by the manufacturers. There is no significant data from other sources at this stage.

Implementation issues

The infrastructure for provision of this therapy is in place and functional throughout the UK and there are no expected issues. No training, facilities or other resources are therefore required, with the possible exception of access to timely resistance testing if this is recommended pre-treatment by the EU license.

Equality

There are no direct expected issues, however it is worth noting that some HCV genotypes disproportionately affect those of specific ethnic minorities or routes of transmission (e.g G4 in Egyptian patients and in MSM).

Treatment Recommendations for the management of patients with Chronic HCV Infection – February 2016

These are recommendations for treatment based on a consensus meeting of experienced treating physicians held in London in January 2016. The most appropriate management of the individual patient is a matter for individual clinical judgement based on patient need taking due account of the evidence base, the NICE completed cost effectiveness analyses and the overall cost of the medication.

Therapies that are NICE approved are presented in bold and those that are NICE unapproved are italicised.

The prices of the different regimens vary considerably. Clinicians should take due regard to the budgetary impact of the drugs selected, taking account of the individual patient's requirements.

Genotype 1

	Non-cirrhotic	Cirrhotic
Treatment-naive	**Sof/Led 8 wks** **[a]Omb/Par +Das+Rib 12 wks** **[b]Omb/Par+Das 12 wks**	**Sof/Led** *+/- Rib* **12[1] wks** ***Omb/Par+ Das+ Rib 12[2,3] wks**
Treatment-experienced	**Sof/Led 12 wks** **[a]Omb/Par+Das+Rib 12 wks** **[b]Omb/Par+Das 12 wks**	**Sof/Led** *+/- Rib* 12[1] wks ***Omb/Par+Das+Rib** *12*/**24[3] wks**
Liver decompensation (NHSE policy, not NICE approved)	*Consider assessment for liver transplantation. Decisions about suitability and timing of antiviral therapy should be undertaken by the MDT in conjunction with the local transplant centre. If treated during decompensation then Sof/Led/Rib 12 wks is appropriate.*	

[a] Genotype 1a
[b] Genotype 1b
[1] Consider ribavirin in patients more likely to have a poor response (e.g. prior null responders)
[2] In patients at low risk of treatment failure ribavirin may be omitted
[3] 24 weeks in genotype 1a prior null responders, otherwise 12 weeks (differs from NICE who recommend 24 weeks for all)
**Child Pugh A only*

Note
Should Elbasvir/Grazoprevir or Sof/Velpatasvir become available during the lifetime of these recommendations, the ODN's would encourage NHS England to make these drugs available within their licensed indications.

Genotype 2

	Non-cirrhotic	Cirrhotic
Treatment-naive	**Peg+Rib 24 wks*** **IFN Intolerant** **Sof + Rib 12 wks**	**Peg+Rib 24 wks** **IFN Intolerant** **Sof+Rib 12 wks**
Treatment-experienced	**Sof+Rib 12 wks**	**Sof+Rib 12 wks**

Liver decompensation (NHSE policy, not NICE approved)	*Consider assessment for liver transplantation. Decisions about suitability and timing of antiviral therapy should be undertaken by the MDT in conjunction with the local transplant centre. If treated during decompensation then SOF/LED/Rib 12 wks is appropriate.*

**12-16 weeks in patients with high chance of good response*

The panel recommends that NHSE be asked to support a policy of Peg/Sof/Rib for IFN sensitive patients with advanced fibrosis (F3) or cirrhosis

Note
Should Sof/Velpatasvir become available during the lifetime of these recommendations, the ODN's would encourage NHS England to make these drugs available within their licensed indications.

GENOTYPE 3

	Fibrosis <F3	Fibrosis = F3	Cirrhotic
Treatment-naive	**Peg+Rib 24 wks** *OR* *Consider waiting for new therapies*[1]	**Peg+Rib 24 wks** IFN intolerant **Sof+Dac +/- Rib** *12* **wks*** *OR* *Consider waiting for new therapies* [1]	**Sof+Peg+Rib 12wks** IFN intolerant **Sof+Dac +/- Rib** *12* **wks***
Treatment-experienced	**Sof+Peg+Rib** OR *Consider waiting for new therapies* [1]	**Sof+Peg+Rib 12wks** IFN intolerant **Sof+Dac+/- Rib 12 wks***	**Sof+Peg +Rib 12wks** IFN intolerant **Sof+Dac +/- Rib 12 wks***
Liver decompensation (NHSE policy, not NICE approved)	*Consider assessment for liver transplantation. Decisions about suitability and timing of antiviral therapy should be undertaken by the MDT in conjunction with the local transplant centre. If treated during decompensation then Sof/Dac/Rib 12 wks is appropriate.*		

The clinicians have recommended that NHSE consider funding Peg+Riba+Sof for patients with F3 fibrosis

**Treatment can be extended to 24 weeks by MDT if there are poor response characteristics at baseline (HIV coinfection, post-OLT cirrhosis) or on treatment (ribavirin intolerance, validated viral load kinetic predictor). The majority of patients will be treated for 12 weeks. (Note that NICE recommends 24 weeks)*

[1] *This recommendation is not based on clinical effectiveness but on the assumption of future acquisition costs. Sof+Dac is a cost effective regimen approved by NICE for patients with advanced fibrosis who cannot have interferon.*

Note
Should Sof/Velpatasvir become available during the lifetime of these recommendations, the ODN's would encourage NHS England to make these drugs available within their licensed indications.

GENOTYPE 4

	Non-cirrhotic		Cirrhotic	
Treatment-naive	**Omb/Par +/-Rib***	**12 wks**	**Sof/Led** **Omb/Par+Rib**	**12 wks** **12 wks**
Treatment-experienced	**Sof/Led** **Omb/Par+Rib**	**12 wks** **12 wks**	**Sof/led** *+/- Rib* **Omb/Par+Rib**	12 wks **24[1] wks**

Liver decompensation (NHSE policy, not NICE approved)	*Consider assessment for liver transplantation. Decisions about suitability and timing of antiviral therapy should be undertaken by the MDT in conjunction with the local transplant centre. If treated during decompensation then Sof/Led/Rib 12 wks is appropriate.*

Note

**In exceptional circumstances, can consider Sof+Dac+RBV or 12W Sof/Led (Not NICE approved), in those patients in whom drug-drug interactions with Omb/Par/Rib are considered a potential concern.*

[1] *For patients who are at low risk of treatment failure consideration should be given to 12 weeks treatment*

Should Elbasvir/Grazoprevir or Sof/Velpatasvir become available during the lifetime of these recommendations, the ODN's would encourage NHS England to make these drugs available within their licensed indications

GENOTYPE 5 AND 6

There are insufficient data to develop a clear consensus at this time. These genotypes are uncommon in England and until more data are available decisions must be made on a case-by-case basis.

We recommend that for interferon tolerant patients Peg/Riba/Sof should be made available and for IFN intolerant patients we recommend that Sof/Led be provided. In the future if Sof/Velpatasvir is available we suggest that NHSE consider making this drug available for these patients.

PATIENTS WITH HIV CO-INFECTION

- All HIV/HCV co-infected patients should be managed by/in conjunction with teams with expertise in co-infection care and pharmacists versed with drug-interactions
- In general, the same DAA-based regimens used in HCV mono-infection are applicable to co-infected patients with chronic HCV
    - Please NOTE mortality benefit from liver and non-liver causes in patients with F0/F1 fibrosis achieving SVR are convincingly demonstrated in this group of patients
    - Higher fibrosis progression rates despite effective cART
    - Exceptions to the general recommendations
        - 8 weeks of therapy with Sof/Led for G1 HCV should only be used in Rx-naïve patients with mild fibrosis and vl <6 million IU/mL
        - For G1 cirrhotic patients addition of Rib to Sof/Led for 12 weeks is recommended
        - For G1a cirrhotic patients – 24 weeks of Omb/Par/Das/Rib is recommended until further data are available
        - For G3 patients with advanced fibrosis/cirrhosis, Sof/Dac/Rib may need to be extended to 24 weeks
- Drug-interactions with antiretrovirals need careful consideration and co-infected patients may need alternate regimens when drug-interactions cannot be overcome
- Patients with acute/early HCV should be offered psychological intervention to minimise risk of onward transmission/re-infection and those failing to demonstrate likelihood of spontaneous resolution should:
    - Where possible be enrolled on to clinical trials in acute/early HCV for shorter duration DAA-based therapy
    - Or offered same treatment regimens as non-cirrhotic chronic HCV/HIV co-infection – recommended with research

- Decision regarding treatments for re-infections should be made at ODN level

FIBROSIS DEFINITIONS

The definition of cirrhosis is a Fibroscan score of >11.5 and F3 a score > 9.5kPa

In centres without ready access to Fibroscan then a FIB-4 level of less than 1.3 makes the presence of F3 fibrosis unlikely. A FIB-4 score of over 1.3 does not confirm F3 but indicates the need for further assessment of fibrosis severity.

Abbreviations

Sof= sofosbuvir
Led = ledipasvir
Omb = Ombitasvir
Par = Paritaprevir
Das = Dasabuvir
Rib = Ribavirin
Peg = pegylated interferon

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: UKCPA
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

What is the expected place of the technology in current practice?
To be considered as an option for all oral treatment for genotypes 1 &4 & possibly 3 if licensed.

Several drug regimens now exist for the treatment of these genotypes. Choice is driven nationally by cost and NHSE as well as individual patient factors. However sometimes clinician choice is over-ridden by cost.

If licensed for genotype 3 patients this will increase treatment options and SVR rates.

Grazoprevir-elbasvir offers the advantage of use in patients with chronic kidney disease and dialysis with good SVR rates which is an advantage over sofosbuvir-ledipasvir.

Good SVR data in patients previously treated with an NS3/4 protease inhibitor which is an advantage over ombitasvir-paritaprevir-ritonavir and dasabuvir.

Potentially longer treatment courses when compared to sofosbuvir-ledipasvir.

Decompensated cirrhotic patient's would be better not being treated with this combination.

Treatment should be delivered as other hepatitis C treatment via specialist MDT at an ODN with out-patient care delivery. Following specialist review and treatment initiation care could theoretically transfer to primary care for completion.

Will need pharmacist interaction review and adherence assessment.

The advantages and disadvantages of the technology

- Will be a useful addition to the drug repertoire – subtle differences depending on individual patient factors that will allow more options to be available for discussion and choice.
- Similar requirements in terms of assessment for drug-drug interactions.
- Potentially shorter drug courses than some options and longer courses than others.
- Increased safety warnings when compared to sofosbuvir-ledipasvir for hepatic impairment.
- No change in clinic capacity
- Potentially additional pre-treatment test for NS5A polymorphisms
- Will require on treatment viral monitoring as currently happens.

As with the majority of hepatitis C trials results will be applicable to our populations with the same genotypes, given accepted differences of trials versus clinical practice differences. Treatment courses will be applicable to a UK setting although genetic variability may influence the usage based on polymorphism tests.

SVR is the outcome of interest and in the future prognosis post SVR will be of interest – however that isn't of relevance to this STA.

This treatment is well tolerated, and not really any different to other all oral combinations. Obviously better tolerated than interferon based regimens. Side effects do occur but are on the less serious end of the scale (nausea, headache, fatigue). Adverse events were lower in those patients not receiving ribavirin. Serious adverse events included a rise in ALT which were generally asymptomatic and resolved.

No real clinical practice data to report.

Any additional sources of evidence
No

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

Delivery would be able to be delivered without any additional resources via existing networks and service specifications provided they are funded and staffed as previously agreed.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Grazoprevir–elbasvir for treating chronic hepatitis [ID842]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Sanjay Bhagani

Name of your organisation ; British HIV Association

Are you (tick all that apply):

a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

Since NICE technology appraisals 363, 364 and 365, IFN-free therapy has become standard of care for the treatment of patients with chronic HCV infection. PegIFN and ribavirin together with sofosbuvir or sofosbuvir and ribavirin in accordance with with TA 330, remains the treatment of choice for the more difficult to treat Genotype 3 infection.
Guidelines from the European Association of the Study of the Liver (EASL) and a consensus statement from BASL/BVHG/BSG and BHIVA outline the ideal choice of agents based on genotype, previous treatment experience and stage of liver disease.

The technology in question (Grazoprevir-Elbasvir) is a useful addition to to the currently available therapies especially for patients with Genotype1/4 and 6 infections and for patients with renal impairment where Sofosbuvir-based therapies are relatively contra-indicated. Moreover, it provides an additional choice of agents to overcome insurmountable drug-drug interactions in some patients. The addition of sofosbuvir may make it a viable alternative IFN-free option for treating Genotype 3 patients.

Patients with end-stage renal disease represent an unmet need in the context of currently available therapies for chronic HCV infection.

Grazoprevir-Elbasvir would be, initially be used in secondary care in hepatology, viral hepatitis and co-infection clinics.

The advantages and disadvantages of the technology

Grazoprevir/Elbasvir would be packaged as a single-tablet regimen and will be similar to other all oral therapies available for HCV treatment.
Depending on the EMA license, there may be a requirement for baseline resistance testing in certain sub-groups (G1a patients with previous pegIFN/ribavirin experience for example) to determine the optimum length of therapy and the need for addition of ribavirin. This may well add a certain complexity to it's use.
There is little experience of it's use outside of Clinical Trials in the UK. The side-effect profile from clinical trials have not raised any particular concern.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

It is very important for the Committee to consider the need of HIV/HCV co-infected patients where liver disease progression is faster and where there has been a clearly demonstration of all-cause mortality benefit in successfully treating HCV in patients with milder stages of hepatic fibrosis.
See Berenguer at al, JAIDS 2014; 66: 280-287

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

See above

Implementation issues

Implementation of NICE guidance (330, 363, 364, 365) is already underway within the infrastructure of ODNs.
This technology will not require any further resource for immediate implementation.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Clinical Commissioning Groups (CCGs) provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a CCG perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: Graham Foster

Name of your organisation Clinical Lead NHSE HCV Operational Delivery Networks. Professor of Hepatology Queen Mary, University of London, Honorary consultant Barts Health NHS Trust

Please indicate your position in the organisation:

- commissioning services for the CCG in general?
- *Clinical lead for NHSE HCV service, lead at Barts Health, provide clinical advise on commissioning for HCV and other liver disorders.*

- commissioning services for the CCG specific to the condition for which NICE is considering this technology?
- *Clinical lead for NHSE HCV service, lead at Barts Health, provide clinical advise on commissioning for HCV and other liver disorders.*

- responsible for quality of service delivery in the CCG (e.g. medical director, public health director, director of nursing)?
- *Responsible locally and nationally for quality of HCV service*

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
  Recognised expert in managing patients with HCV

- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
- *Participated in clinical trials and led many of the pivotal trials in HCV*

- other (please specify)

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Single Technology Appraisal (STA)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Therapy for chronic HCV infection is delivered by operational delivery networks which ensure that there is uniform access to treatment throughout the country. Regional variation in access is monitored and corrected.

At present access to therapy for HCV is provided in line with NICE guidance and according to a prioritisation process with local clinical leads determining local priorities guided by national recommendations.

The choice of drug is determined by clinical need and the drug cost and where clinically equivalent drugs are available clinicians are encouraged to choose the most clinically cost effective option and where more expensive options are deemed necessary support from a knowledgeable clinical colleague is required.

The current alternatives to the therapy under consideration include sofosbuvir/ ledipasvir, sofosbuvir/daclatasvir and ombitasvir/parateprevir/dasabuvir. Interferon based therapies are still used in the populations under consideration where clinically acceptable and where costs are favourable.

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

This technology is currently not being used in any health authority in England but this position is under review by NHS England following a tendering process that has recently been undertaken.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

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Single Technology Appraisal (STA)

As per previous responses to guidance related to directly acting antivirals NHS England would expect NICE to recommend that such treatments should be delivered within the Operational Delivery Networks.

A positive guidance will give clinicians a further option for patients for specific genotypes in place of current NICE approved therapies. The new technology has some advantages over existing therapies and provides welcome clinical choice that will allow clinicians to personalise therapy to the benefit of patients with hepatitis C.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

NHS England would expect the technology to be deployed alongside existing treatments and used within the Operational Delivery Networks where treatment can be supervised by experienced clinicians but delivered locally, close to the patient by the most appropriate health care professional.

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions)

If the drug is marketed at a lower cost than existing therapies then for patients in whom this technology is indicated the therapy will be widely used and result in significant cost savings, allowing more patients with HCV to undergo therapy. If the drug is marketed at a higher cost than it is likely that clinicians will chose a less costly, equally effective alternative. The product is likely to be available at a commercial in confidence discount following a recent tender commissioned by the Commercial Medicines Unit.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

Access to directly acting antivirals is welcomed but as highlighted in previous responses funding such therapies places a significant financial burden on the NHS in England. NHS England's aim is to reduce ongoing costs in relation to hepatitis C by significantly reducing the number of patients who develop cirrhosis, decompensated liver disease and liver cancer. If access is allowed outside the current Operational Delivery Networks then there could be significant resources required which may need to be removed from other planned services.

Would there be any need for education and training of NHS staff?

Not if the therapy is delivered through the Operational Delivery Networks

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

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- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

If the therapy is delivered by Operational Delivery Networks equity of access will be monitored by NHS England and interventions introduced to correct any inequity that may develop

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

NHS England would ask NICE to consider an MTA of the available treatments in the near future.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Grazoprevir–elbasvir for treating chronic hepatitis [ID842]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Prof Anna Maria Geretti
Chair of Virology and Infectious Diseases; Honorary Consultant in Infectious Diseases

Name of your organisation

University of Liverpool
Institute of Infection and Global Health

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? Member of the BASL and BHIVA
- other? (please specify) Co-lead regional HCV ODN

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Chronic hepatitis C is treated within the context of Operational Delivery Networks – which implement centrally developed directives about eligibility for treatment and treatment options. These directives reflect cost-benefit evaluations as well as general affordability. Patients with certain characteristics are able to receive IFN-free regimens. Others can currently access traditional IFN-based therapy. Data from other countries with large numbers of treated subjects show that cure rates with IFN-free regimens are high (>90%) in routine clinical practice. A small subset of patients experience treatment failure, reflecting a combination of issues related to the treatment choice, adherence and compliance with care, advanced liver disease, and possibly other viral or host determinants.

Overall, at present there is limited variation in practice across England. The major factor that guide treatment decisions include: HCV genotype, previous therapy, whether the patient is eligible to receive interferon, and presence or absence of cirrhosis. Recent directives from NHS-E have delegated certain treatment decisions to the ODNs thus creating potential for some degree of variation to emerge where consensus is not developed and consistently applied. There is currently variation across the UK when comparing England with Scotland for instance.

There are some areas of uncertainty concerning strategies to optimise outcomes within the allowed treatment options: Examples include:

- Duration of therapy in some patients
(e.g., naïve, Gt1, non-cirrhotic, candidate to receive HARVONI for 8 weeks: uncertainties concerning the influence of a high pre-treatment viral load, or in HIV-positive patients with moderate fibrosis or drug-induced portal hypertension; Cirrhotic, GT3, candidate to receive DAC/SOF/RBV for 12 weeks where some experts would recommend 24 weeks)
- Use of PI-based regimens (Abbvie ProD currently) in subjects that are PI-exposed where a resistance test or stored sample to demonstrate PI resistance is not available
- Treatment strategies for acute HCV (including deferral and trial access outside of London
- How to manage treatment failure on IFN-free regimens in general (e.g., drug resistance testing is recommended widely in international guidelines but there is no agreed strategy for the UK at present about who should be tested, how, where, and when)
- Re-treatment strategies for subjects who fail therapy with IFN-free regimens
- Role of RBV in patients where there are risk factors for non-response to IFN-free therapy (e.g., high viral load; drug resistance)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

- Impact of dosing schedules on adherence (e.g., with HARVONI vs. ProD for Gt1) particularly in settings such as prisons
- Management of Gt3 patients who are not in urgent need for treatment (treat or defer)
- Patients with renal disease
- Patients who experience re-infection after initial cure
- Optimal time to measure SVR (e.g., role of SVR4 in capturing relapse early; need for further measurements past SVR12)
- Definition of IFN intolerance
- Predictors of liver events in patients with Child Pugh A cirrhosis on ProD and safe use of the regimen in this group, including the related safety monitoring requirements in the first 4 weeks of therapy

Grazo/Elb (+/- RBV) offers an effective treatment option for patients with Gt1 or Gt4, including those with cirrhosis or HIV; clinical trials show cure rates >94%. For Gt1a the US label recommends pre-treatment screening for resistance (NS5a) to decide on length of treatment and use of RBV. The major advantages of Grazo/Elb include safety in advanced renal disease, single tablet formulation, high efficacy in Gt4 (>96%), activity in PI-experienced patients (first gen PIs), activity in cirrhosis without rbv. The need to perform a baseline resistance test may be regarded as either cumbersome or an opportunity to tailor treatment based on patients' characteristics (as done routinely in HIV infection). It may support improved use of other strategies as well (e.g., deciding on shorter treatment duration or addition of RBV with HARVONI Gt1 with high viral load).

Alternative available strategies are HARVONI and ProD (or PegIFN + RBV + SOF).

HARVONI is efficacious and available as a single tablet, with best experience currently gained in the context of Gt1. It can be used in patients with decompensated liver disease, but has safety issues related to pre-existing advanced renal disease, and with concomitant use of other agents with potential renal toxicity in the presence of moderate renal impairment. Treatment can be shortened from 12 to 8 weeks in patients with favourable pre-treatment characteristics but there remain some uncertainties about defining risk factors for failure . RBV is typically added in patents with cirrhosis. There is some potential for drug interactions, most notably with PPIs.

ProD is similarly efficacious. RBV is typically added in cirrhosis. It is a multi-dose twice-daily treatment with moderate to high potential for drug-drug interactions. It is contraindicated in patients with decompensated cirrhosis/Child-Pugh B and C. There are some uncertainties about risk of liver events in Child-Pugh A.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Prognosis is primarily affected by liver fibrosis and pre-treatment history. There are virus- and host-related factors that also play a role, so that overall prognosis in terms of treatment responses is the expression of multiple determinants (e.g., pre-existing drug resistance is more likely to have an impact in the context of advanced liver

disease and suboptimal adherence; certain host genetic factors modulate the impact of certain drug resistance mutations).

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Best used in specialist clinics at the beginning, comprising specialist viral hepatitis clinics within hepatology / Infectious Diseases. If resistance-testing pre-treatment is adopted, the site must have access to appropriate testing and virology interpretation. Current ODN structure provides a forum for discussion of cases. Treatment could also be provided in settings such prisons, community centres etc. under the governance of the oDN.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

NA

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

Please refer to the ASLD Guidelines (http://www.hcvguidelines.org/full-report/initial-treatment-hcv-infection) April 2016 version.

Grazo/Elb recommended for:

Gt1a, naive, non-cirrhotic or compensated cirrhosis, no baseline NS5A resistance mutations (IA)

If RAVs are present, use for 16 weeks with RBV [IIa B]

Gt1b, naive, non-cirrhotic or compensated cirrhosis [IA]

Gt4 naive, non-cirrhotic or compensated cirrhosis [IIa B]

EASL is currently updating the guidelines and a new version is expected in July 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

This is an effective single tablet regimen. Advantages are the lack of requirement for RBV in compensated cirrhosis, high efficacy in Gt4, and good safety in advanced renal disease.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The introduction of pre-treatment resistance testing for NS5A to inform treatment selection appears to offer a way to tailor treatment as it would inform use of other regimens (e.g., duration, use of RBV).

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Clinical trials are sufficiently representative.

In addition to the routine response evaluations, the studies have demonstrated high efficacy in compensated cirrhosis, in subjects with significant renal impairment, and in subjects with previous PI exposure. The impact of pre-treatment resistance has been evaluated.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Not recommended for decompensated cirrhosis. There have been no safety warnings to date to my knowledge.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Data presented at the recent EASL Conference (Apr 2016)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

This would represent an additional treatment option that will allow strategies to be optimised for patients, specifically for those with Gt1 and Gt4, with and without compensated cirrhosis and with emphasis to be placed on use in renal impairment. Resources required include the availability of resistance testing for Gt1a to tailor duration and use of RBV. The infrastructure is widely available in the UK and easily accessible. Several NHS labs have already established the protocols.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Grazoprevir–elbasvir for treating chronic hepatitis C

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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None for the authors. Dr Ryder attended paid advisory boards for MSD but has no other conflict of interest.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in blue 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.

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Contributions of authors
Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, contributed to the writing of the report and supervised the health economic part of the project. Nasuh Büyükkaramikli, Tim Kanters and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Regina Leadley and Debra Fayter 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. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

2D	Ombitasvir–paritaprevir–ritonavir
3D	Ombitasvir–paritaprevir–ritonavir with dasabuvir
3D/RBV	Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin
AASLD	American Association for the Study of Liver Diseases
AE	Adverse Events
ART	Antiretroviral treatment
BASL	British Association for the Study of Liver
BHIVA	British HIV Association
BI	Budget impact
BIC	Bayesian information criterion
BOC	Boceprevir
BOC/PR	Boceprevir in combination with pegylated-interferon alfa and ribavirin
BORR	Best overall response rate
BSC	Best supportive care
C	Cirrhotic
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CHC	Chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic kidney disease
CMU	Commercial medicines unit
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSR	Clinical study report
CUA	Cost utility analysis
DAA	Direct-acting antivirals
DAE	Discontinuation due to adverse events
DCV	Daclatasvir
DCV/PR	Daclatasvir in combination with pegylated-interferon alfa and ribavirin
DCV/SOF	Daclatasvir in combination with sofosbuvir
DCV/SOF/RBV	Daclatasvir in combination with sofosbuvir, with ribavirin
DoH	Department of Health
EASL	European Association for the Study of Liver
EBR/GZR	Grazoprevir/elbasvir
ECG	Electrocardiogram
EMA	European Medicines Agency
eRVR	Extended rapid viral response
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
EQ-5D-5L	European Quality of Life-5 Dimensions, five-level scale
ERG	Evidence Review Group
ESRD	End stage renal disease
EUR	Erasmus University Rotterdam
EVR	Early viral response

FAS	Full analysis set
FDA	Food and Drug Administration
5-FU	5-Fluorouracil
GT	Genotype
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV/HIV-1	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
IC	Indirect Comparison
ICD	International Classification of Diseases
ICER	Incremental Cost-effectiveness Ratio
ICTRP	International Clinical Trials Registry Platform
IFN	Interferon
ISPOR	International Society for Pharmacoecomics and Outcomes Research
ITT	Intention to Treat
IU	International unit
IV	Intravenous
KSR	Kleijnen Systematic Reviews
LDV	Ledipasvir
LDV/SOF	Ledipasvir in combination with sofosbuvir
LYS	Life Year Saved
MCMC	Markov Chain Monte Carlo
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MS	Manufacturer's Submission
MSD	Merck Sharp and Dohme
MTC	Mixed Treatment Comparison
NA	Not applicable
NC	Non-cirrhotic
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not Reported
NS5A	Non-structural protein 5A
OAE	Overall adverse events
OS	Overall survival
OST	Opiate substitution therapy
P	Pegylated-interferon alpha
PCR	Polymerase chain reaction
PR	Pegylated-interferon alpha in combination with ribavirin
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
PWIDs	People who inject drugs

QALY(s)	Quality-adjusted Life Year(s)
QoL	Quality of life
RAVs	Resistance-associated variants
RBV	Ribavirin
RCGP	Royal College of General Practitioners
RCT	Randomised Controlled Trial
RNA	Ribonucleic acid
RR	Relative Risk; Risk Ratio
SAE	Serious Adverse Events
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard deviation
SF-36	Short form 36
SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMV	Simeprevir
SMV/PR	Simeprevir in combination with pegylated-interferon alfa and ribavirin
SOF	Sofosbuvir
SOF/RBV	Sofosbuvir in combination with ribavirin
SOF/PR	Sofosbuvir in combination with ribavirin, with pegylated-interferon alfa
SVR	Sustained virologic response
STA	Single Technology Appraisal
TBC	To Be Confirmed
TE	Treatment-experienced
TN	Treatment-naïve
TVR	Telaprevir
TVR/PR	Telaprevir in combination with pegylated-interferon alfa and ribavirin
UK	United Kingdom
UMC	University Medical Centre
WHO	World Health Organization
WTP	Willingness to pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) presents an evaluation of the clinical effectiveness and cost effectiveness of grazoprevir/elbasvir (EBR/GZR) for the treatment of chronic hepatitis C (CHC). The decision problem addressed by the CS was not completely in line with the final scope issued by the National Institute for Health and Care Excellence (NICE) with respect to the comparators. In particular, boceprevir and telaprevir are not included in the decision problem because these treatment regimens are no longer representative of current clinical practice according to the company.

The CS only presents the results for two subgroups (GT1 and GT4 patients); none of the analyses undertaken within the CS relate to patients with GT2, GT3, GT5 or GT6. The ERG notes that this is consistent with the wording of the EPAR, which only relates to GT1 and GT4 patients. The CS assumes that GT4 are similar to GT1 patients.

The company's model does not include the development of resistance to EBR/GZR; the CS states that resistance-associated variants (RAVs) was not considered in post hoc analyses and therefore do not support the economic analyses.

1.2 Summary of clinical effectiveness evidence submitted by the company

Fifty publications, representing 40 clinical trials were included in the CS. Fifteen of these publications, representing eight clinical trials, involved EBR/GZR; six out of eight EBR/GZR studies are RCTs, and 25 out of 32 comparator studies are RCTs. The remaining nine studies are either non-randomised controlled studies or single arm studies.

From the six included EBR/GZR RCTs, two studies have no relevant control arms. For study C-EDGE-TE control arms that include ribavirin and those of 16 weeks duration are excluded in the CS, leaving only one arm to be included. For study C-EDGE CO-STAR control arms that include ribavirin and those of eight or 18 weeks duration are excluded in the CS, leaving only four arms to be included, all of these evaluated the same intervention: EBR /GZR for 12 weeks. From the remaining four studies, three included a placebo arm, and one trial had an active comparator: SOF/PR for 12 weeks.

The EBR/GZR trials included patients with GT1, 3, 4 and 6; treatment naïve, experienced and mixed patient populations; mixed fibrosis status; and patients with 'no HIV' (C-EDGE TN, C-SURFER and C-EDGE H2H), chronic kidney disease (C-SURFER), or 'on opiate substitution therapy' (C-EDGE CO-STAR).

SVR rates for EBR/GZR for 12 weeks ranged from 91% to 97% for GT1a, from 98% to 100% for GT1b and from 67% to 100% for GT4 infections. The NMA revealed no statistically significant differences between the SVRs achieved with EBR/GZR and the other direct-acting antiviral (DAA) regimens (LDV/SOF, 3D/±RBV, and DCV/SOF) in any of the subgroups that were investigated. The results of the naïve comparison and NMA were broadly consistent, especially for the all-DAA regimens.

Results from the NMA showed either results significantly in favour of EBR/GZR (for all GT1 treatment-naïve populations) when compared to PR or SMV/PR or no significant difference when

compared to SOF/PR, LDV/SOF, 3D/RBV and DCV/SOF. For GT4, the only significant difference was EBR/GZR versus PR for treatment-naïve patients.

According to the company, EBR/GZR has a favourable safety and tolerability profile when compared with placebo or active control (SOF/PR) for the treatment of patients with HCV GT1 and GT4 infections, irrespective of cirrhosis stage or treatment experience. The most commonly reported AEs included fatigue, headache, nausea, and in some cases diarrhoea, dizziness, and cough. Across all studies discontinuation rates related to drug-related AE or SAE were rare. Similarly, the rates of haematological abnormalities were also low, with a trend of increased anaemia associated with the use of RBV.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

It is unlikely that trials of EBR/GZR relevant to the final NICE scope were missed.

The conclusion from the EBR/GZR trials is that EBR/GZR has high SVR rates, especially for patients with GT1a and GT1b. In addition, EBR/GZR has a relative favourable safety and tolerability profile, especially when compared with P and/or RBV containing regimens.

Comparator data (for SVR12) were provided by single arms of randomised controlled trials (RCTs), or non-RCTs. Although reported baseline characteristics appear similar between intervention and comparator trials, the possibility that other factors differed across trials cannot be ruled out. The ERG has serious problems with the methodology of both types of evidence synthesis performed by the company and considers the outcomes of these analyses therefore as unreliable. The main problem with the naïve comparisons is that individual arms of included studies were pooled and compared directly with each other. This ignores the randomisation within the trials and thus the heterogeneity between studies. The main concern with the NMA is that within some of the NMA analyses, most of the PR data were imputed, not just for a few trials. Therefore, these analyses are largely based upon fictitious data.

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 EBR/GZR compared to various comparators: PR, BSC, SOF/PR, SMV/PR, 2D, 3D, LDV/SOF and DCV. The cost effectiveness analysis resembled previous STAs for HCV treatments in many aspects. The population in the cost effectiveness analysis was divided into 12 subpopulations. Patients were divided into three genotypes (GT; GT1a, GT1b and GT4); treatment experience (treatment naïve and treatment experienced); and divided according to cirrhosis status (cirrhotic and non-cirrhotic patients).

Results were presented as incremental to PR treatment, as the NMA did not reveal significant differences between EBR/GZR and other all-DAA treatments. A National Health Service (NHS) and Personal and Social Services (PSS) perspective was adopted with a lifetime time horizon. Discount rates used for costs and quality-adjusted life years (QALYs) were 3.5%

The cost effectiveness model was a Markov model consisting of 13 health states. Non-cirrhotic patients in the model start in states F0-F3, and cirrhotic patients in the model start in state F4 (compensated cirrhosis). Patients then may either remain in their current health state or move to a more severe health state of liver disease. After reaching compensated cirrhosis, patients are assumed to have a risk of developing decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), which would possibly lead to liver transplantation. In the model, after a successful treatment, it is

assumed that patients achieve SVR, and patients who do not achieve SVR are at the same risk of disease progression as untreated patients.

Treatment effectiveness was modelled in terms of SVR rates. Other treatment specific model input parameters were treatment duration, discontinuation and treatment-related adverse event rates. All other clinical inputs were not treatment related. NMAs were performed in order to identify the appropriate SVR, discontinuation and AE rates for EBR/GZR and its comparators. Because only limited data was available for GT4 patients, data for GT1a patients was used for these patients.

Utility values were derived from a study published by Wright et al., 2006. In addition to health state utilities, age-dependent utility decrements were included, based on utility values of the general UK population. Furthermore, treatment-specific utility decrements were included to assess adverse events. Utility increments for SVR were based on the study by Wright et al., 2006.

List prices for EBR/GZR and comparator treatments were used in the cost effectiveness analysis. Besides drug acquisition costs, costs for monitoring and follow-up and costs related to adverse events were included in the cost effectiveness analysis, all based on previous studies.

In all subgroups, PR was the treatment that resulted in minimum costs. For GT1a and GT4 populations, ICER (compared to PR) values for EBR/GZR were around £9,000 per QALY gained for TN and around £8,000 per QALY gained for TE patients. For GT1b, in the TN populations, ICER (compared to PR) values were around £8,000 per QALY gained, whereas for the TE populations, ICER values were about £6,000 per QALY gained. From the full incremental analysis (presented in an appendix to CS), EBR/GZR appeared to be cost effective only in GT1a TN C, GT1a TE C and GT4 TE C populations. In all other populations, EBR/GZR was either dominated by the other cost effective interventions, or the ICER values compared to the previous cost effective interventions were above the £20,000 per QALY gained threshold.

Next to the base-case analyses, probabilistic sensitivity analyses and scenario analyses were conducted. Deterministic sensitivity analyses showed that the following input parameters had the largest influence on the ICER: utility value used for the F4 health state, starting age in the model, drug costs of EBR/GZR and of comparators, SVR of EBR/GZR, and RR of the SVR of the comparators.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

In the health economic analysis, BOC/PR and TVR/PR and SMV/SOF treatments were not considered as a comparator, as they were not part of the current clinical practice according to the company.

Some of the populations mentioned in the final scope (e.g. HIV co-infected patients or interferon ineligible) were excluded from the cost effectiveness analysis. 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 are disputable. Furthermore, heterogeneity of the treatment experienced population was not taken into account (e.g. patient may be intolerant or inadequate responder to the previous therapy, or a patient may have already received a DAA treatment, or maybe DAA naïve, EBR/GZR may have different effectiveness in each of these groups).

In the model it was assumed that non-cirrhotic patients recover from their fibrosis levels completely in time, and therefore, after reinfection, they start disease without fibrosis (F0). The ERG finds this assumption not plausible, since there is no clinical consensus on this and no evidence was provided by the company.

Another drawback of the modelling approach was its static structure; a dynamic modelling approach might have reflected the decrease in reinfection rates in the population level.

NMAs were performed in order to identify the appropriate SVR, discontinuation and AE rates for EBR/GZR and its comparators. Because only limited data was available for GT4 patients, data for GT1a patients was used for these patients. In addition to NMA, the company also provided analysis based on indirect naïve comparison data.

The ERG has concerns on the plausibility of both approaches, which are not in line with the evidence synthesis best practices and are susceptible to bias.

Other disease progression related transition probabilities were not dependent on the treatment, however some sources were older than 10 years, and may be outdated.

The utilities from RCTs could have been used by the company in their cost effectiveness analysis instead of the utilities from the literature. The baseline utility of the HCV patients in the trials were higher than the utilities in the literature. On the other hand, measured utility increment after SVR in the trials were smaller than the reported values in the literature. The ERG has methodological concerns on how the disutilities due to AEs and how the age based utility decrements were applied in the model.

The ERG was unsure about the completeness of the health state cost estimates used in the model, and thinks that the cost effectiveness analysis based on list prices may not reflect the actual value for money of the HCV treatments.

The ERG is concerned about the validation status of the cost effectiveness analysis by the company. No details were given concerning the expert validation by the external health economist as well as by the clinical specialists, and no validation exercises such as cross-validation, validation against external data, or validation against internal data had been conducted.

Based on the uncertainties in the CS base-case, the ERG created a new base-case by not assuming full recovery from fibrosis after SVR, and by applying SVR utility increase estimate derived from RCTs, and by not implementing the age based utility decrements.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4 using a good range of databases and grey literature resources. The CS and response to clarification provided sufficient details for the ERG to appraise the searches.

The company's submitted evidence on clinical effectiveness broadly covered the final scope set out by NICE. The review of EBR/GZR trials included all relevant trials in which EBR/GZR had been used. Reviews for other treatments were likely to have identified the majority of trials of other

relevant treatments. The submission covers the key clinical outcomes, including SVR rates, adverse events and mortality.

The economic model structure reflects the main aspects of the chronic HCV disease.

1.6.2 Weaknesses and areas of uncertainty

Search terms for the most commonly used comparator, pegylated-interferon alfa with ribavirin (PR), were not included in the clinical effectiveness strategies. Clinical effectiveness searches were limited to English language only, and the cost effectiveness search employed for NHS EED included unnecessary study design filters.

The main concern regarding clinical effectiveness is that comparator data (for SVR12 and AEs) were provided by single arms of randomised controlled trials (RCTs), or non-RCTs. Although reported baseline characteristics appear similar between intervention and comparator trials, the possibility that other factors differed across trials cannot be ruled out. Therefore, the ERG has serious problems with the methodology of both types of evidence synthesis performed by the company and considers the outcomes of these analyses as unreliable.

The cost effectiveness analyses were based on the treatment effectiveness data and all health economic analyses thus suffered from the uncertainty of evidence synthesis, as well. Furthermore all analyses were conducted on list prices, which may not reflect the actual value for money of the treatments.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Based on the uncertainties in the base-case of the company, the ERG created a new base-case by not assuming full recovery from fibrosis after SVR, and by applying SVR utility increase estimates derived from RCTs and by not implementing the age based utility decrements.

The findings of the ERG base-case analysis are generally in line with those from the CS. For GT1a and GT4 populations, ICER (compared to PR) values for EBR/GZR were around £8,000-£9,000 per QALY gained for cirrhosis patients and around £11,000-£12,000 per QALY gained for non-cirrhosis patients. For GT1b, in the TN and NC populations, the ICER (compared to PR) was almost £13,000 per QALY gained, whereas for the other GT1b populations, ICER values were around £8,000 per QALY gained.

From the full incremental analysis, EBR/GZR appeared to be cost effective only in GT1a TN C, GT1a TE C and GT4 TE C populations. In the GT4 TN C population, EBR/GZR resulted in an ICER around the £20,000 per QALY gained threshold, and in all other populations, EBR/GZR was either dominated by the other cost effective interventions, or the ICER values compared to the other cost effective interventions were above the £20,000 per QALY gained threshold.

Findings from the exploratory PSA and scenario analyses conducted by ERG were also comparable to the CS base-case. Choice of the evidence synthesis approach and using GT4 specific data for GT4 subgroup had significant impacts on the ICER across all groups, using time based disease progression transition probabilities has a significant impact on non-cirrhotic patients and having shorter time horizons changes the ICER to a great extent.

On the whole, EBR/GZR seems to be cost effective compared to PR in all subgroups. However, when all comparators are considered in the full incremental analysis, it is cost effective only in GT1a TN C, GT1a TE C and GT4 TE C populations both in the analyses from the company and the ERG. However, these results should be interpreted with caution, as they were based on list prices and treatment effectiveness parameters that were based on questionable assumptions/methods.

2 BACKGROUND

This report provides a review of the evidence submitted by Merck Sharp & Dohme Limited (MSD) in support of grazoprevir/elbasvir (EBR/GZR: tradename Zepatier®) for the treatment of chronic hepatitis C for both treatment naïve and previously treated patients.[1] The background section of the report by the ERG outlines and critiques the company's description of the underlying health problem and the overview of current service provision.[1]

2.1 Critique of company's description of underlying health problem.

The underlying health problem of this appraisal is hepatitis C described in the CS as a 'blood-borne virus that primarily causes infection of the liver.'[1] The company further states that 'around 90% of new HCV infections in UK (England) are in people who inject drugs (PWIDs).'[1]

The company appraisal, as per the NICE scope[2] is related to patients with chronic hepatitis C which the company states occurs in up to 80% of those with acute Hepatitis C virus (HCV) infection.[1]

ERG comment: Reliable sources are cited to support these statements. The ERG notes that no definition of 'chronic HCV' is provided but assumes it to be six months after acute infection.[3]

The risks of hepatitis C, both when treated and untreated, are outlined in the CS. The company states that 21% of those with chronic infection go on to develop cirrhosis and that 2 to 4% of those with chronic HCV and cirrhosis also develop hepatocellular carcinoma (HCC.)[1] The company further states that 'HCV patients are at increased risk of developing chronic kidney disease (CKD) and end-stage renal disease (ESRD) compared to patients not infected with HCV'.[1]

ERG comment: Reliable sources are used to support these statements. The figure of 21% is taken from a NICE costing template for various related TAR appraisals.[4]

The burden of disease is described in the CS. The company cites that 'In the UK, an ~214,000 individuals are chronically infected with HCV, of which ~160,000 people are infected in England alone.'[1] The prevalence of the various genotypes in the UK is presented. 'In the UK, GT1 and GT3 are equally distributed accounting for 90% of HCV infected patients, GT2 for 6%, GT4 for 4% and, GT5 and GT6 for less than 1%.'[1]

ERG comment: Prevalence data are taken from Public Health England documentation.[5] The prevalence of HCV in Wales is not explicitly cited. It is noted that the prevalence of GT1 according to Public Health England estimates is 47% (alongside GT4 the focus of the drug under appraisal).[5]

The company states that sustained virological response at 12 weeks (SVR12) 'is now considered the gold standard' to determine HCV cure rates.[1]

ERG comment: No specific time frame of sustained virological response was specified in the NICE scope.[2] This statement was based on a retrospective analysis of five trials (779 patients with genotypes 1 to 6) that found that 777 of the patients (99.7%) with SVR12 also had SVR24. Advice from our clinical experts confirmed that SVR12 (and SVR24) is generally considered to represent cure.

The company states that 'Patients have a lower quality of life (QoL) compared with the general population. Fatigue and depression are common in these patients, with lower mental and physical component summary scores compared to individuals not infected with HCV.'

The company also notes the limited data on life expectancy in HCV-infected individuals but cites an English cohort study reporting 'standardised mortality ratios three times higher than those expected in the general population. The increased risk of mortality was attributed to liver-related causes, and those patients with a drug-using lifestyle.'[1]

ERG comment: The potential effect of the disease on patients with HCV has been appropriately considered.

2.2 Critique of company's overview of current service provision

The company states 'NICE recently communicated (29th February 2016) that the proposed Hepatitis C clinical guideline has been put on hold with a publication date still to be confirmed. NICE has stated that technology appraisals (TA) continue to evaluate new pharmacological therapies and the role of the clinical guideline will be re-considered when these have been produced.'[1]

ERG comment: In the absence of a NICE guideline in a changing treatment landscape, the company summarises the relevant TAR appraisals as per the scope.[2] The company also references European Association for the Study of the Liver (EASL) guidelines and UK consensus guidelines on HCV.[6, 7]

The company references the NHS England clinical commissioning policy (CCP) statement on the treatment of chronic hepatitis C in patients with cirrhosis.[8] They state that 'it is unclear whether the recent NICE TAs will supersede the existing NHSE CCP.' They note the establishment of the operational development networks (ODN) by NHSE to organise access to treatments.[1]

ERG comment: The NHSE CCP states that it 'is an interim policy statement that will be reviewed in line with the NICE technology appraisal guidance schedule.' The policy statement covers commissioning criteria for treatment of chronic hepatitis C in patients with cirrhosis and those with advanced liver disease.[8]

The company states that 'The current clinical pathway of care takes into consideration multiple sources of information.' and 'Treatment choice is multifactorial and takes into account the: viral genotype and subtype, stage of liver disease, cirrhosis status, treatment experience, and previous therapy regimens.'[1]

The company states 'Current treatment options include established treatments, such as pegylated-interferon alpha (P), telaprevir (TVR), and boceprevir (BOC); all of which are recommended by NICE and are summarised in Table 16 of the CS. Most recently NICE have recommended the use of sofosbuvir (SOF), simeprevir (SMV), daclatasvir (DCV), ledipasvir in combination with sofosbuvir (LDV/SOF), and ombitasvir–paritaprevir–ritonavir with (3D) or without dasabuvir (2D) within specific patient populations. These treatment options are stratified by treatment experience, cirrhosis stage, and GT subtype.'[1]

ERG comment: The complexity of the changing treatment landscape is appropriately outlined by the company.

The company states that. 'EBR/GZR is an oral, once daily single FDC tablet regimen for the treatment (cure) of HCV in patients with GT1a, GT1b, or GT4 infections. EBR/GZR can be administered for 12 weeks irrespective of treatment experience and cirrhosis stage.'[1]

The company add that 'EBR/GZR represents an IFN- and RBV-free treatment option for the majority of adult patients. It is anticipated that EBR/GZR will represent a preferred treatment option to IFN-containing regimens, including pegylated-interferon alpha (P), SOF/P, and SMV'.[1]

ERG comment:

- EBR/GZR is positioned in the current pathway alongside other treatments for GT1 and GT4 subtypes but has no restriction related to treatment experience and cirrhosis stage.
- On 26 May 2016 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Zepatier, intended for the treatment of chronic hepatitis C. It stated that 'The benefit with Zepatier when used with or without ribavirin is its very high efficacy against HCV genotypes 1 and 4 including in patients with compensated cirrhosis and severe kidney disease. The most common side effects are fatigue and headache.'[9]
- The role of EBR/GZR as a preferred treatment option to IFN-containing regimens will be considered in this appraisal in relation to the effectiveness and adverse events.

The company states that '….it is estimated that only 28,000 patients in England were treated between 2006 and 2011. This represents 3% of those chronically infected per year.'[10]

The company describes the budgetary impact of increased testing and diagnosis of HCV in the UK.[11] With reference to a cohort simulation model the company notes 'an increase in healthcare costs, from ~£82.7million in 2012 to ~£115 million in 2035' with associated productivity losses.[11]

ERG comment: The company appropriately highlights impacts on future service provision and budgeting.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the manufacturer)

	Decision problem outlined in final scope issued by NICE[2]	Decision problem addressed in the company submission[1]	Additional comments
Population	People with chronic hepatitis C: • Who have not had treatment for chronic hepatitis C (CHC) (treatment-naïve) • Who have had treatment for chronic hepatitis C (treatment-experienced)	The CS focuses solely on subgroups of patients with GT1 and GT4. Most of the data relate to patients with GT1 disease. The ERG notes that the wording of the SmPC[12] relates to patients with GT1 and GT4 disease.	In addition the company notes that the anticipated product label does not differentiate between treatment-naïve/treatment-experience, cirrhotic/non-cirrhotic HCV patients.
Intervention	Grazoprevir/elbasvir	Grazoprevir/elbasvir for 12 weeks.	This is in accordance with the scope and the SmPC.[12]
Comparator (s)	• best supportive care (watchful waiting) (GT1-6) • boceprevir in combination with pegylated-interferon alfa and ribavirin (for GT1 only) • daclatasvir in combination with pegylated-interferon alfa and ribavirin (for specific people with GT4; as recommended by NICE) • daclatasvir in combination with sofosbuvir, with or without ribavirin (for specific people with GT1, 3 or 4; as recommended by NICE) • ledipasvir–sofosbuvir (for specific people with GT1 or 4; as recommended by NICE) • ombitasvir–paritaprevir–ritonavir with or without dasabuvir or ribavirin (for GT1 or 4) • pegylated-interferon alfa with ribavirin (for GT1-6) • simeprevir in combination with pegylated-interferon alfa and ribavirin (for GT1 or 4)	• best supportive care (watchful waiting) (GT1 and GT4) • daclatasvir in combination with ribavirin, with or without pegylated-interferon alfa (GT4) • daclatasvir in combination with sofosbuvir, with or without ribavirin (GT1 and GT4) • ledipasvir–sofosbuvir with or without ribavirin (GT1 and GT4) • ombitasvir/paritaprevir/ritonavir with or without dasabuvir (GT1 and GT4) • pegylated-interferon alfa with ribavirin (GT1 and GT4) • simeprevir in combination with pegylated-interferon alfa and ribavirin (GT1 and GT4) • sofosbuvir in combination with ribavirin, with or without pegylated-interferon alfa (for specific people with GT1 and GT4; as	Mostly in line with the final scope, albeit with some discrepancies (see Section 3.3). The company notes that "best supportive care" is defined as no treatment in their submission. The ERG notes that the wording of the SmPC relates to patients with GT1, and GT4 disease. In addition, boceprevir and telaprevir are not included in the decision problem because these treatment regimens are no longer representative of current clinical practice according to the company.

	Decision problem outlined in final scope issued by NICE[2]	Decision problem addressed in the company submission[1]	Additional comments
	• sofosbuvir in combination with ribavirin, with or without pegylated-interferon alfa (for specific people with GT1-6; as recommended by NICE) • telaprevir in combination with pegylated-interferon alfa and ribavirin (for GT1 only)	recommended by NICE)	
Outcomes	The outcome measures to be considered include: • sustained virological response • development of resistance to grazoprevir–elbasvir • mortality • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • sustained virological response • mortality • adverse effects of treatment • health-related quality of life.	In line with the final scope. The company states that RAVS was not considered in post hoc analyses and therefore do not support the economic analyses.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	In line with the final scope. The company's submitted model evaluates costs and health gains (reported as incremental costs per quality-adjusted life year) from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon.
Subgroups to be considered	If evidence allows the following subgroups will be considered: • genotype • people with renal impairment • co-infection with HIV	Analyses are provided on the following subgroups: • genotype • people with and without cirrhosis • response to previous treatment (non-	Separate subgroup analyses are not presented for people with renal impairment, patients who are co-infected with HIV, people with advanced liver disease, post-

	Decision problem outlined in final scope issued by NICE[2]	Decision problem addressed in the company submission[1]	Additional comments
	• people with and without cirrhosis • people with advanced liver disease • post-liver transplantation • people with haemoglobinopathies (for example, sickle cell disease, thalassaemia major) • response to previous treatment (non-response, partial response, relapsed) • people who are intolerant to or ineligible for interferon treatment	response, partial response, relapsed)	liver transplantation, people with haemoglobinopathies and people who are intolerant to or ineligible for interferon treatment.
Special considerations including issues related to equity or equality	None stated	None stated	In line with the final scope.

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 (treatment-naive) or who have had treatment for chronic hepatitis C (treatment-experienced).

On 26 May 2016 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Zepatier, (Grazoprevir-elbasvir) intended for the treatment of chronic hepatitis C.[9, 13]

The full indication is: "Zepatier is indicated for the treatment of chronic hepatitis C (CHC) in adults (see sections 4.2, 4.4 and 5.1). For hepatitis C virus (HCV) genotype-specific activity see sections 4.4 and 5.1."

The summary of product characteristics (SmPC) specifies that grazoprevir/elbasvir is recommended for treatment of chronic hepatitis C infection in patients with or without compensated cirrhosis (Child-Pugh A only) and for HCV genotypes 1a, 1b and 4.[12]

Detailed recommendations as described in the SmPC are as follows[12]:

- ALT elevations - Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated.
- The efficacy of ZEPATIER has not been demonstrated in HCV genotypes 2, 3, 5 and 6. ZEPATIER is not recommended in patients infected with these genotypes.
- The efficacy of ZEPATIER in patients previously exposed to ZEPATIER, or to medicinal products of the same classes as those of ZEPATIER (NS5A inhibitors or NS3/4A inhibitors other than telaprevir, simeprevir, boceprevir), has not been demonstrated (see Section 5.1 of the SmPC).
- Co-administration of ZEPATIER and OATP1B inhibitors, CYP3A or P-gp inducers is contraindicated and the concomitant use of ZEPATIER and strong CYP3A inhibitors is not recommended.
- The safety and efficacy of ZEPATIER have not been studied in HCV/HBV co-infected patients.
- ZEPATIER is not recommended for use in children and adolescents under 18 years of age because the safety and efficacy have not been established in this population.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take ZEPATIER.

3.2 Intervention

The intervention described in the final scope is grazoprevir/elbasvir. According to the CHMP, Zepatier is a fixed dose combination of two direct acting antivirals, elbasvir and grazoprevir (ATC code: J05AX68). It will be available as film-coated tablets (containing 50 mg elbasvir and 100 mg grazoprevir). Elbasvir is an inhibitor of the hepatitis C virus (HCV) NS5A protein, while grazoprevir is an inhibitor of the HCV NS3/4A protease. Both proteins are essential for viral replication.

The SmPC specifies that grazoprevir/elbasvir is recommended for treatment of chronic hepatitis C infection in patients with or without compensated cirrhosis (Child-Pugh A only) and for HCV genotype:[12]

- 1a: ZEPATIER for 12 weeks; (ZEPATIER for 16 weeks plus ribavirinA should be considered in patients with baseline HCV RNA level >800,000 IU/ml and/or the presence of specific NS5A

polymorphisms causing at least a 5-fold reduction in activity of elbasvir to minimise the risk of treatment failure (see Section 5.1 of the SmPC)).

- 1b: ZEPATIER for 12 weeks.
- 4: ZEPATIER for 12 weeks; (ZEPATIER for 16 weeks plus ribavirinA should be considered in patients with baseline HCV RNA level >800,000 IU/ml to minimise the risk of treatment failure (see Section 5.1 of the SmPC)).

3.3 Comparators

The comparators described in the final scope are as follows:

- best supportive care (BSC; watchful waiting) (genotypes 1-6)
- boceprevir in combination with pegylated-interferon alfa and ribavirin (BOC/PR; for genotype 1 only)
- daclatasvir in combination with pegylated-interferon alfa and ribavirin (DCV/PR; for specific people with genotype 4; as recommended by NICE)
- daclatasvir in combination with sofosbuvir, with or without ribavirin (DCV/SOF or DCV/SOF/RBV; for specific people with genotype 1, 3 or 4; as recommended by NICE)
- ledipasvir in combination with sofosbuvir (LDV/SOF; for specific people with genotype 1 or 4; as recommended by NICE)
- ombitasvir–paritaprevir–ritonavir with or without dasabuvir or ribavirin (2D, 3D, or 3D/RBV; for genotype 1 or 4)
- pegylated-interferon alpha in combination with ribavirin (PR; for genotypes 1- 6)
- simeprevir in combination with pegylated-interferon alfa and ribavirin (SMV/PR; for genotype 1 or 4)
- sofosbuvir in combination with ribavirin, with or without pegylated-interferon alfa (SOF/RBV or SOF/PR; for specific people with genotypes 1-6; as recommended by NICE)
- telaprevir in combination with pegylated-interferon alfa and ribavirin (TVR/PR; for genotype 1 only)

As grazoprevir–elbasvir is not recommended for HCV genotypes 2, 3, 5 and 6, these genotypes can be ignored. In addition, the company made the following changes:

- "best supportive care" is defined as no treatment.
- boceprevir (BOC) and telaprevir (TVR) are excluded from the decision problem as these treatment regimens are no longer deemed representative of current clinical practice.

3.4 Outcomes

The CS[1] includes the following outcomes, all of which are specified in the final NICE scope[2]:

- SVR
- Mortality
- Adverse effects of treatment
- HRQoL

The CS does not include one of the outcomes specified in the NICE scope,[2] that is, the development of resistance to grazoprevir/elbasvir, stating that this outcome was not considered in post hoc analyses and therefore does not support the economic analyses. Clinical advice received by the ERG suggests that this end point reflects treatment failure other than that from not taking pills. Given the high SVR rates this outcome may therefore be less relevant.

3.5 Other relevant factors

The decision problem addressed by the CS[1] includes consideration of the following subgroups, all of which were specified in the final NICE scope[2]:

- Genotype
- People with and without cirrhosis
- Response to previous treatment (non-response, partial response, relapsed)

Separate subgroup analyses are not presented for people with renal impairment, patients who are co-infected with HIV, people with advanced liver disease, post-liver transplantation, people with haemoglobinopathies and people who are intolerant to or ineligible for interferon treatment.

No special considerations including issues related to equity or equality have been specified in the submission.

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, was used to inform this critique.[14] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[15] The ERG has presented only the major limitations of each search strategy in the main report.

CLINICAL EFFECTIVENESS

The CS states that a systematic literature review (SLR) was conducted to identify relevant studies to inform both direct and indirect comparisons between EBR/GZR and comparators for the treatment of chronic hepatitis C (CS, Section 4.1.1).

Searches were reported for MEDLINE, MEDLINE In-Process, Embase and the Cochrane Register of Controlled Trials (CENTRAL), and were undertaken in January 2016. In addition online congress abstracts for the annual meetings of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) were searched for the last two years (2014-2015). Searches of the International Clinical Trials Registry Platform (ICTRP) were also undertaken. These meet the requirements specified in current best practice guidance as detailed in the NICE guide to the methods of technology appraisal. [16] Search strategies for the database searches were provided in Appendix 2 of the CS and are well reported and reproducible. Strategies for the AASLD meeting were not included in the CS, however further details of searches conducted were provided following a clarification request.

The database searches were clearly structured and used combinations of index terms appropriate to the resource searched, free text and a large number of synonyms for the condition, intervention and most of the comparators, although the use of tradenames (such as Zepatier) may have formed a useful addition to the search. Search terms were not included for pegylated-interferon alpha or ribavirin. Following a clarification request, the company stated that:

'The clinical effectiveness search strategies were informed by the chosen methodology for the indirect treatment comparison i.e. network meta-analysis with imputed controls. Peginterferon alfa with ribavirin (PR) was selected as the most suitable treatment to base the imputation on, as it is the most commonly used active control in trials of the newer direct acting antiviral (DAA) treatments. The statistical analysis plan restricted the PR data used in the imputation of controls for each NMA to comparative trials featuring a PR arm and at least one other intervention of interest. The rationale for this was that these trials would be balanced in terms of effect modifiers for regimens containing interferon, but that may not influence outcomes for all DAA regimens. As a result, it was not necessary to identify trials where PR was the primary intervention.'

The ERG believes that the search would have been more comprehensive, with a reduced likelihood of missing relevant records, if terms for PR, the most commonly used comparator, had been included in the strategy, particularly as these terms were included in the cost effectiveness searches (CS, Section 5.1.1; CS, Appendix 12).

Terms were used to limit results to randomised and non-randomised trials only; using an adapted version of the Scottish Intercollegiate Guidelines Network (SIGN) search filter. The host provider for each database was listed, and the date span of the databases searched and the specific date the searches were conducted were provided.

The ERG has some concerns that the searches were limited to English language only. Current best practice states that 'Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'.[17] The ERG is concerned that restricting to English language has the potential to miss relevant material.

Indirect and mixed treatment comparisons
The clinical effectiveness searches reported in Section 4.1 of the CS and Appendix 2 of the CS were used to inform the indirect and mixed treatment comparisons. As the searches included a facet of relevant comparators the ERG considered the searches fit for purpose, although inclusion of search terms for PR would have resulted in a more comprehensive search.

Non-randomised and non-controlled evidence
The clinical effectiveness searches reported in Section 4.1 of the CS and Appendix 2 of the CS were used to identify non-randomised and non-controlled evidence. As the searches included a facet of relevant comparators the ERG considered the searches fit for purpose, although inclusion of search terms for PR would have resulted in a more comprehensive search.

Adverse events
The clinical effectiveness searches reported in Section 4.1 of the CS and Appendix 2 of the CS were used to identify studies reporting safety data. As the searches included a facet of relevant comparators the ERG considered the searches fit for purpose, although inclusion of search terms for PR would have resulted in a more comprehensive search.

SUMMARY OF SEARCHING
The searches in the CS were well documented and easily reproducible; searches were carried out in line with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[16]

4.1.2 Inclusion criteria
The company used one set of inclusion criteria for intervention trials and comparator trials. The inclusion criteria are outlined in Table 4.1 (see CS Table 20, page 55).

Table 4.1: Hierarchical inclusion/exclusion criteria for the review

Rank	Clinical effectiveness criteria	Reason for inclusion	Reason for exclusion	Hierarchy of exclusion rationale
1	Language	English only	Other languages	Non-English language publications were expected to include populations not relevant to the decision problem.
2	Study design	Randomised controlled trials and controlled clinical trials with at least one arm assessing an intervention of interest, non-randomized clinical trials, including single-arm prospective clinical trials assessing an intervention of interest	Review, editorial, letter, comment, meta-analysis, phase 1 studies, in-vitro studies	See comment in the 'Statement of decision problem' relating to comparators.
3	Populations	Not chronically infected with HCV genotypes 1 or 4, not adult population (≥18 years of age)	Not chronically infected with HCV genotypes 1 or 4, not adult population (≥18 years of age)	EBR/GZR is not licensed for use outside of these populations.
4	Interventions	Interferon-free regimens: EBR/GZR (+/- RBV) LDV/SOF +/- RBV 2D or 3D +/- RBV DCV/SOF +/- RBV SOF/RBV Interferon-containing regimens: DCV/PR BOC/PR TVR/PR SMV/PR SOF/PR	Other DAA combinations, with or without PR	Studies were not excluded based on dose or duration at the literature search stage. However, in the indirect treatment comparison only trial arms with NICE approved regimens were included.
5	Outcomes	SVR12, SVR24, DAE, OAE, anaemia, pruritus, nausea, neutropenia, rash, thrombocytopenia.	RVR, eRVR, vRVR, EVR	SVR at 12 and 24 weeks post treatment are the primary efficacy outcomes in trials of treatments for HCV.
5	Comparators	All	None	Single arm studies were also included, as were studies comparing

Rank	Clinical effectiveness criteria	Reason for inclusion	Reason for exclusion	Hierarchy of exclusion rationale
				different regimens of the same DAA combination.

Abbreviations: BOC, boceprevir; DAA, direct acting antiviral; DAE, discontinuation related to AE; DCV, daclatasvir; DAS, dasabuvir; EBR, Elbasvir; eRVR, extended rapid viral response; EVR, early viral response; GZR, grazoprevir; LDV, ledipasvir; OAE, overall adverse events; HCV, hepatitis C virus; PAR/r, paritaprevir/ritonavir; PR, pegylated-interferon alpha and ribavirin; R, ribavirin; RVR, rapid viral response; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TVR, telaprevir; vRVR, very rapid viral response.

ERG comment: These inclusion criteria match the decision problem set out within the final NICE scope[2] in terms of the population and the intervention. It is not clear from the list of interventions whether interferon-containing regimens in combination with ribavirin were included. However, as all possible comparators are included, these regimens should also be included. The only major limitation is that there is a language restriction: only English language publications are included.

Two reviewers conducted study selection (see CS page 54); this is in line with good practice. The study selection process was provided in a flow diagram of study selection (see CS Figure 1, page 57) that indicates that 50 publications, representing 40 clinical trials were included; 15 of these publications, representing eight clinical trials involved EBR/GZR. These studies are presented in Table 4.2. As can be seen in the table, six out of eight EBR/GZR studies are RCTs, and 25 out of 32 comparator studies are RCTs. The remaining nine studies are either non-randomised controlled studies or single arm studies.

From the six included EBR/GZR RCTs, two studies have no relevant control arms. For study C-EDGE-TE control arms including ribavirin and of 16 weeks duration are excluded, leaving only one arm to be included. For study C-EDGE CO-STAR control arms including ribavirin and of eight or 18 weeks duration are excluded, leaving only four arms to be included, all of these evaluated the same intervention: EBR/GZR 1-12.

Table 4.2: Included studies

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
EBR/GZR RCTs						
1	Merck & Co, 2015[18]	C-EDGE TN, NCT02105467	Double blind, Randomised, Multicentre (N=421)	Genotype: 1, 4, 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: EBR/GZR 1-12	Arm 2: Placebo 1-12, 13-16 Unblinding, EBR/GZR 17-28
2	Kwo et al., 2015[19]	C-EDGE TE, NCT02105701	Open label, Randomised, Multicentre (N=420)	Genotype: 1, 4, 6 Treatment history: Experienced Fibrosis status: Mixed	Arm 1: EBR/GZR 1-12 Arm 2: EBR/GZR/RBV 1-12	Arm 3: EBR/GZR 1-16 Arm 4: EBR/GZR/RBV 1-16
3	Merck & Co, 2015[20]	C-SURFER, NCT02092350	Double blind, Randomised, Multicentre (N=235)	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: Chronic kidney disease (defined as glomerular filtration rate ≤ 29), no HIV	Arm 1: EBR/GZR 1-12 Arm 2: EBR/GZR 1-12	Arm 3: Placebo 1-12, 13-16 Unblinding, EBR/GZR 17-28
4	Merck & Co, 2015[21]	C-WORTHY, NCT01717326	Open label, Randomised, Multicentre (N=573)	Genotype: 1 or 3 Treatment history: Mixed Fibrosis status: Mixed Other characteristics:	Arm 1: EBR/GZR/RBV 1-12 Arm 2: EBR/GZR/RBV 1-12 Arm 3: EBR /GZR 1-12 Arm 4: EBR/GZR/RBV 1-8 Arm 5: EBR/GZR/RBV 1-12 Arm 6: EBR/GZR 1-12 Arm 7: EBR/GZR/RBV 1-12 Arm 8: EBR/GZR 1-12 Arm 9: EBR/GZR/RBV 1-18 Arm 10: EBR/GZR 1-18	Arm 11: EBR/GZR/RBV 1-12 Arm 12: EBR/GZR 1-12 Arm 13: EBR/GZR/RBV 1-18 Arm 14: EBR/GZR 1-18 Arm 15: EBR/GZR/RBV 1-12 Arm 16: EBR/GZR 1-12 Arm 17: EBR/GZR/RBV 1-

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
						8 Arm 18: EBR/GZR 1-8 Arm 19: EBR/GZR/RBV 1-12 Arm 20: EBR/GZR/RBV 1-18
5	Dore et al., 2015[22]	C-EDGE CO-STAR, NCT02105688	Double blind, Randomised, Multicentre (N=301)	Genotype: 1, 4, 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: On opiate substitution therapy (OST) for at least 3 months	Arm 1: EBR/GZR 1-12	Arm 2: Placebo 1-12, 13-16 Unblinding, EBR/GZR 17-28
6	Merck & Co, 2016[23]	PN077 (C-EDGE H2H)	Open label, Randomised, Multicentre (N=257)	Genotype: 1, 4, 6 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: EBR/GZR 1-12	Arm 2: SOF/PR 1-12
Comparator RCTs						
7	Sulkowski et al., 2014[24]	A1444040, NCT01359644	Open label, Randomised, Multicentre (N=211)	Genotype: 1, 2, 3 Treatment history: Mixed Fibrosis status: Mixed	Arm 1: SOF 1, DCV/SOF 2-24 Arm 2: DCV/SOF1-24 Arm 3: DCV/SOF/RBV 1-24 Arm 4: SOF 1, DCV/SOF 2-24 Arm 5: DCV/SOF 1-24	Arm 6: DCV/SOF/RBV 1-24 Arm 7: DCV/SOF 1-12 Arm 8: DCV/SOF/RBV 1-12 Arm 9: DCV/SOF 1-24 Arm 10: DCV/SOF/RBV 1-24
8	Jacobson et al., 2011[25]	ADVANCE, NCT00627926	Double blind, Randomised, Multicentre	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed	Arm 1: TVR/PR 1-12, PR 13-24 or PR 13-48	Arm 2: TVR/PR 1-8, PR 9-24 or PR 9-48; Arm 3: PR 1-48

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
			(N=1095)			
9	Wyles et al., 2015[26]	ALLY-2, NCT02032888	Open label, Randomised, Multicentre (N=203)	Genotype: Any Treatment history: Mixed Fibrosis status: Mixed Other characteristics: Patients with HIV-1 infection, HCV RNA ≥10,000 IU/mL	Arm 1: DCV/SOF 1-12	Arm 2: DCV/SOF 1-8 Arm 3: DCV/SOF 1-12
10	Kowdley et al., 2013[27]	ATOMIC, NCT01329978	Open label, Randomised, Multicentre (N=332)	Genotype: 1, 4, 5, 6, or indeterminate Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SOF/PR 1-12 Arm 2: SOF/PR 1-24	Arm 3: SOF/PR 1-12, SOF 13-24 or SOF/RBV13-24
11	Hézode et al., 2015[28]	COMMAND-4, AI444042	Double blind, Randomised (N=124)	Genotype: 4 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HCV RNA >10,000 IU/ml	Arm 1: DCV/PR 1-24 or DCV/PR 1-24, PR 25-48	Arm 2: PR 1-48
12	Gane et al., 2014[29]	ELECTRON, NCT01260350	Open label, Randomised, Multicentre (N=173)	Genotype: 1, 2, 3 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 50,000 IU/mL, no HIV	Arm 1: SOF/RBV1-12 Arm 2: SOF/PR 1-4, SOF/RBV 5-12 Arm 3: SOF/PR 1-8, SOF/RBV 9-12 Arm 4: SOF/PR 1-12 Arm 5: SOF 1-12 Arm 6: SOF/PR 1-8	Arm 7: SOF/RBV1-12 Arm 8: SOF/RBV1-12 Arm 9: LDV/SOF/RBV 1-12 Arm 10: LDV/SOF/RBV 1-6 Arm 11: LDV/SOF/RBV 1-12 Arm 12: LDV/SOF 1-12 Arm 13: LDV/SOF/RBV 1-12

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
13	Afdhal et al., 2014[30]	ION-1, NCT01701401	Open label, Randomised, Multicentre (N=865)	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: LDV/SOF 1-12 Arm 2: LDV/SOF/RBV 1-12	Arm 3: LDV/SOF 1-24 Arm 4: LDV/SOF/RBV 1-24
14	Afdhal et al., 2014[31]	ION-2, NCT01768286	Open label, Randomised, Multicentre (N=440)	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: LDV/SOF 1-12 Arm 2: LDV/SOF/RBV 1-12	Arm 3: LDV/SOF 1-24 Arm 4: LDV/SOF/RBV 1-24
15	Kowdley et al., 2014[32]	ION-3, NCT01851330	Open label, Randomised, Multicentre (N=647)	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: LDV/SOF 1-8	Arm 2: LDV/SOF/RBV 1-8 Arm 3: LDV/SOF 1-12
16	Lawitz et al., 2014[33]	LONESTAR, NCT01726517	Open label, Randomised, Single-centre (N=100)	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 10,000 IU/mL	Arm 1: LDV/SOF 1-8 Arm 2: LDV/SOF/RBV 1-8	Arm 3: LDV/SOF 1-12 Arm 4: LDV/SOF 1-12 Arm 5: LDV/SOF/RBV 1-12
17	Dore et al., 2016[34]	MALACHITE-I, NCT01854697	Open label, Randomised, Multicentre (N=311)	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: 3D/RBV 1-12 Arm 2: TVR/PR 1-12, PR 13-24 or PR 13-48 Arm 3: 3D/RBV 1-12	Arm 4: 3D 1-12 Arm 5: TVR/PR 1-12, PR 13-24 or PR 13-48
18	Dore et al., 2016[34]	MALACHITE-II, NCT01854528	Open label, Randomised, Multicentre (N=154)	Genotype: 1 Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: 3D/RBV 1-12	Arm 2: TVR/PR 1-12, PR 13-24 or PR 13-48

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
19	Mizokami et al., 2015[35]	NCT01975675	Open label, Randomised, Multicentre (N=341)	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: No HIV, HCV RNA ≥ 100,000 IU/mL	Arm 1: LDV/SOF 1-12	Arm 2: LDV/SOF/RBV 1-12
20	Hezode et al., 2015[36]	PEARL-I, NCT01685203	Open label, Randomised, Multicentre (N=267)	Genotype: 1b or 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA level > 10,000 IU/mL, No HIV, BMI ≥ 18 and < 38 kg/m2	Arm 1: 2D 1-12 Arm 2: 2D/RBV 1-12 Arm 3: 2D/RBV 1-12 Arm 4: 2D 1-12	Arm 5: 2D 1-12 Arm 6: 2D 1-24 Arm 7: 2D 1-24
21	Andreone et al., 2014[37]	PEARL-II, NCT01674725	Open label, Randomised, Multicentre (N=186)	Genotype: 1b Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: 3D/RBV 1-12	Arm 2: 3D 1-12
22	Ferenci et al., 2014[38]	PEARL-III, NCT01767116	Double blind, Randomised, Multicentre (N=419)	Genotype: 1b Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: 3D/RBV 1-12	Arm 2: 3D 1-12
23	Ferenci et al., 2014[38]	PEARL-IV, NCT01833533	Double blind, Randomised, Multicentre (N=305)	Genotype: 1a Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: 3D/RBV 1-12	Arm 2: 3D 1-12
24	Pearlman et al., 2015[39]	NCT02168361	Open label, Randomised,	Genotype: 1a Treatment history: Mixed	Arm 1: SMV/SOF 1-12	Arm 2: SOF/PR 1-12

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
			Single-centre (N=93)	Fibrosis status: Cirrhosis Other characteristics: No HIV		
25	Fried et al., 2013[40]	PILLAR, NCT00882908	Double blind, Randomised, Multicentre (N=386)	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV RNA > 100,000 IU/mL, no HIV	Arm 1: SMV/PR1-12, PR 13-24 or PR 13-48 Arm 2: SMV/PR1-24 or SMV/PR1-24, PR 25-48	Arm 3: SMV/PR1-12, PR 13-24 or PR 13-48 Arm 4: SMV/PR1-24 or SMV/PR1-24, PR 25-48 Arm 5: PR 1-48
26	Forns et al., 2014[41]	PROMISE, NCT01281839	Double blind, Randomised, Multicentre (N=393)	Genotype: 1 Treatment history: Experienced Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SMV/PR1-12, PR 13-24 or PR 13-48	Arm 2: PR 1-48
27	Jacobson et al., 2014[42]	QUEST-1, NCT01289782	Double blind, Randomised, Multicentre (N=394)	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SMV/PR1-12, PR 13-24 or PR 13-48	Arm 2: PR 1-48
28	Manns et al., 2014[43]	QUEST-2, NCT01290679	Double blind, Randomised, Multicentre (N=391)	Genotype: 1 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: SMV/PR1-12, PR 13-24 or PR 13-48	Arm 2: PR 1-48
29	Feld et al., 2014[44]	SAPPHIRE-I, NCT01716585	Double blind, Randomised, Multicentre (N=636)	Genotype: 1 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: 3D/RBV 1-12	Arm 2: Placebo 1-12, 3D/RBV 13-24
30	Zeuzem et al., 2014[45]	SAPPHIRE-II, NCT01715415	Double blind, Randomised, Multicentre (N=395)	Genotype: 1 Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics: HCV	Arm 1: 3D/RBV 1-12	Arm 2: Placebo 1-12, 3D/RBV 13-24

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
				RNA > 10,000 IU/mL, no HIV		
31	Poordad et al., 2014[46]	TURQUOISE-II, NCT01704755	Open label, Randomised, Multicentre (N=381)	Genotype: 1 Treatment history: Mixed Fibrosis status: Cirrhosis Other characteristics: HCV RNA > 10,000 IU/mL, no HIV	Arm 1: 3D/RBV 1-12	Arm 2: 3D/RBV 1-24
EBR/GZR non-randomised studies						
32	Merck & Co, 2015[47]	C-SCAPE, NCT01932762	Open label, Non-randomised, Multicentre (N=38)	Genotype: 2, 4, 5, 6 Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: No HIV	Arm 1: EBR/GZR/RBV 1-12	Arm 2: EBR/GZR 1-12
Comparator non-randomised studies						
33	Osinusi et al., 2015[48]	ERADICATE, NCT01878799	Open label, Non-randomised, Single-centre (N=50)	Genotype: 1a, 1b, or mixed 1a/1b Treatment history: Naïve Fibrosis status: No cirrhosis Other characteristics: HIV co-infected	Arm 1: LDV/SOF 1-12	Arm 2: LDV/SOF 1-12
34	Moreno et al., 2015[49]	RESTORE, NCT01567735	Open label, Non-randomised, Multicentre (N=107)	Genotype: 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA >10,000 IU/mL, no HIV	Arm 1a: SMV/PR1-12, PR 13-24 or PR 13-48 Arm 1b: SMV/PR1-12, PR 13-24 or PR 13-48	Arm 1c: SMV/PR1-12, PR 13-24 or PR 13-48 Arm 1d: SMV/PR1-12, PR 13-24 or PR 13-48
35	Kohli et al., 2015a[50]	SYNERGY, NCT01805882	Open label, Non-randomised, Multicentre	Genotype: 1 or 4 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV	Arm 1: LDV/SOF 1-12 Arm 2: LDV/SOF 1-12	Arm 3: LDV/SOF 1-12 Arm 4: LDV/SOF 1-12

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
			(N=55)	RNA ≥ 2,000 IU/mL		
EBR/GZR Single arm studies						
36	Rockstroh et al., 2015[51]	C-EDGE CO-INFECTION, NCT02105662	Open label, Non-randomised (N=218)	Genotype: 1, 4, 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: HIV co-infected	Arm 1: EBR/GZR 1-12	
Comparator single arm studies						
37	Lim at al., 2015[52]	NCT02021656	Open label, Non-randomised, Multicentre (N=178)	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: HCV RNA ≥ 10,000 IU/mL, no HIV	Arm 1: LDV/SOF 1-12	
38	Lawitz et al., 2013[53]	NEUTRINO, NCT01641640	Open label, Non-randomised, Multicentre (N=328)	Genotype: 1, 4, 5, 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics:	Arm 1: SOF/PR 1-12	
39	Pol et al., 2015[54]		Open label, Non-randomised, Multicentre (N=80)	Genotype: 1 Treatment history: Experienced Fibrosis status: No cirrhosis Other characteristics:	Arm 1: SOF/PR 1-12	
40	Rodriguez-Torres et al., 2015[55]	NCT01565889	Open label, Non-randomised,	Genotype: Any Treatment history: Naïve Fibrosis status: No cirrhosis	Arm 1: SOF/PR 1-12	

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
			Single-centre (N=23)	Other characteristics: HIV-1 co-infected		

Source: CS, Appendix 9, Table 1, page 178

Note: Highlighted green=excluded, see Appendix 4, page 95.

Abbreviations: BOC, boceprevir; DAS, dasabuvir; DCV, daclatasvir; EBR/GZR, grazoprevir/elbasvir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, Pegylated interferon and ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naïve; TVR, telaprevir.

4.1.3 Critique of data extraction

For HRQoL studies, data extraction was performed independently by two reviewers (CS, Section 5.4.3, page 205); and for cost studies data extraction was performed by a single reviewer (CS, Section 5.5.2, page 223). For effective studies it is not explicitly stated how many reviewers were involved in the data extraction process. It is stated in the CS that "within the included trials there are treatment arms that are not relevant to the scope of this submission and are not considered further" (CS, Section 4.2, page 58).

4.1.4 Quality assessment

Table 27 in Section 4.6 of the CS[1] provided quality assessment of the EBR/GZR trials only. Appendix 6 of the CS[56] provided quality assessment of all 40 included clinical trials and supporting text. The Cochrane Collaboration Risk of Bias tool[57] was used to assess validity of the included trials. The CS acknowledges that the use of the Cochrane tool for assessment of validity of non-randomised trials is not appropriate however it is used on one non-RCT study namely C-EDGE CO-INFECTION.[58] It is unclear how the quality assessment was carried out.

ERG comment: The ERG confirms that the Cochrane risk of bias tool is appropriate for the quality assessment of randomised controlled trials (RCTs). Assessment should be carried out independently by two individuals; however this cannot be confirmed by the text in Appendix 6.[56]

Table 4.3 shows the comparison of the quality assessment as carried out in the CS[1] and by the ERG. C-EDGE TN[18] and C-SURFER[20] are reported in the CS to have low risk of bias for all domains. C-EDGE CO-STAR[59] is reported to have unclear risk of bias for selection bias (allocation concealment) and low risk of bias for all other domains.

ERG comment: The clinical study report for C-EDGE CO-STAR[59] states "Randomization occurred centrally using an interactive voice response system (IVRS)/ integrated web response system (IVRS/IWRS).[59]" Therefore the ERG judged this to be low risk of selection bias (allocation concealment).

C-EDGE H2H[23] was low risk of bias for selection (random sequence generation), attrition and reporting bias but high for performance and detection bias and unclear for selection bias (allocation concealment).

ERG comment: The clinical study report for C-EDGE H2H[23] states "Randomization occurred centrally using an interactive voice response system (IVRS)/ integrated web response system (IVRS/IWRS)". Therefore the ERG judged this to be low risk of selection bias (allocation concealment).

Table 4.3: Comparison of quality assessment of relevant RCTs by CS and ERG

TRIAL	C-EDGE CO-STAR[59]		C-EDGE TN[18]		C-SURFER[20]		C-EDGE H2H[23]	
	CS	ERG	CS	ERG	CS	ERG	CS	ERG
Selection bias (Random sequence generation)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Selection bias (Allocation concealment)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Performance bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk
Detection bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk
Attrition bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Reporting bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Other bias	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk

The included RCTs are similar in that they have similar outcomes (SVR12, SVR24, PRO) over 12 and up to 24 weeks. The study populations however are different. C-EDGE Co-STAR has a study population who are all on opiate substitution therapy (OST) and treatment naïve (TN) and most are non-cirrhotic (79.4%).[59] Genotypes 1a, 1b, 4 and 6 are all represented with the majority being GT1a (75.7%). C-EDGE H2H has a mostly non-cirrhotic population (82.9%) and mostly treatment naive (75%).[23] Although, genotype 1a, 1b and 4 are represented, in this trial the majority population is GT1b at 82%.[23] C-EDGE TN and C-SURFER are probably the most comparable in terms of study population. The majority of participants are non-cirrhotic and TN with a similar balance of GT1a and GT1b (50.1% vs 51.9% and 40.6% vs 47.7%[18, 20]). In addition, C-EDGE TN has a small proportion of GT4 (6.2%) and GT6 (3.1%) participants.[18]

ERG comment: It is difficult to compare studies when there is such a variation in the study population. Presenting results per sub-group population would be helpful and allow the studies to be more comparable.

4.1.5 Evidence synthesis

The company states that "as C-EDGE H2H was the only head-to-head trial featuring EBR/GZR, a traditional pairwise meta-analysis was not carried out."

ERG comment: The ERG agrees that a meta-analysis of EBR/GZR trials is not feasible. Only one of these trials had an active comparator (C-EDGE H2H). In addition, three EBR/GZR trials had a placebo control arm, but these were all in different patient populations: treatment naïve patients (C-EDGE TN), patients with chronic kidney disease (C-SURFER) and patients on opiate substitution therapy (C-EDGE CO-STAR). Therefore, there is too much heterogeneity between the study populations to perform a reliable meta-analysis.

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, only four comparative EBR/GZR trials have been included in the submission. Therefore, we will only describe these four EBR/GZR RCTs (see Table 4.4) in terms of trial methodology (see Table 4.5) and baseline characteristics (see Table 4.6).

Table 4.4: Included comparative EBR/GZR trials

	Reference, author year	Trial number/acronym,	Trial design/phase	Population	Intervention	Comparator
EBR/GZR RCTs						
1	Merck & Co, 2015[18]	C-EDGE TN, NCT02105467	Double blind, Randomised, Multicentre (N=421)	Genotype: 1, 4, 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: EBR/GZR 1-12	Arm 2: Placebo 1-12, 13-16 Unblinding, EBR/GZR 17-28
2	Merck & Co, 2015[20]	C-SURFER, NCT02092350	Double blind, Randomised, Multicentre (N=235)	Genotype: 1 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: Chronic kidney disease (defined as glomerular filtration rate ≤ 29), no HIV	Arm 1: EBR/GZR 1-12 Arm 2: EBR/GZR 1-12	Arm 3: Placebo 1-12, 13-16 Unblinding, EBR/GZR 17-28
3	Dore et al., 2015[22]	C-EDGE CO-STAR, NCT02105688	Double blind, Randomised, Multicentre (N=301)	Genotype: 1, 4, 6 Treatment history: Naïve Fibrosis status: Mixed Other characteristics: On opiate substitution therapy (OST) for at least 3 months	Arm 1: EBR/GZR 1-12	Arm 2: Placebo 1-12, 13-16 Unblinding, EBR/GZR 17-28
4	Merck & Co, 2016[23]	PN077 (C-EDGE H2H)	Open label, Randomised, Multicentre (N=257)	Genotype: 1, 4, 6 Treatment history: Mixed Fibrosis status: Mixed Other characteristics: No HIV	Arm 1: EBR/GZR 1-12	Arm 2: SOF/PR 1-12

Abbreviations: EBR/GZR, grazoprevir/elbasvir; PR, Pegylated interferon and ribavirin; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naive

Table 4.5: Comparative summary of trial methodology for comparative EBR/GZR RCTs

Criteria	C-EDGE TN[18] NCT02105467	C-SURFER[20] NCT02092350	C-EDGE CO-STAR[59] NCT02105688	C-EDGE H2H[23] NCT02358044
Study location	• 60 study centres • 10 counties; Australia, Czech Republic, France, Germany, Israel, Puerto Rico, South Korea, Sweden, Taiwan, and the United Sates	• 68 Study centres • 12 countries; USA, Argentina, Australia, Canada, Estonia, France, Israel, South Korea, Lithuania, Netherlands, Spain, and Sweden	• 55 study centres • 14 countries; USA, UK, Spain, Australia, Canada, France, Romania, Taiwan, Germany, Norway, Puerto Rico, New Zealand, Netherlands, Israel	• 32 study centres • 9 countries: Czech Republic, Denmark, Hungary, Lithuania, Norway, Poland, Romania, Spain, and Turkey
Trial design	• Phase III • Randomised, double blind controlled (patients, study investigator, and sponsor personnel blinded) • Cross over treatment arm	• Phase III • Randomised, double blind controlled (patients blind, study administrator blind) • Cross over treatment arm, which was open-label treatment arm (deferred group to EBR/GZR)	• Phase III • Randomised, double blind immediate treatment group (placebo controlled) • Parallel group, cross over to open-label active therapy	• Phase III • Open label, randomised active control trial
Eligibility criteria	• Chronic HCV GT1, 4, or 6 • Treatment naïve patients • Cirrhotic or non-cirrhotic • Aged ≥18 years • HCV≥10,000IU/mL at screening	• Chronic HCV GT1 • Treatment naïve or prior treatment failure with IFN or PEG-IFN or PR intolerant • Cirrhotic or non-cirrhotic • Aged ≥18 years • CKD stages 4-5 (with or without haemodialysis) • HCV≥10,000IU/mL at screening	• Chronic HCV GT1, 4, or 6 • Treatment naïve • Cirrhotic or non-cirrhotic • Aged ≥18 years • HCV≥10,000IU/mL at screening • HIV HCV co-infected patients	• Chronic HCV GT1, GT4, or GT6 • Treatment naïve or experienced • Cirrhotic or non-cirrhotic • Aged ≥18 years • HCV≥10,000IU/mL at screening
Trial drugs (intervention,	Intervention • EBR(50mg)/GZR(100mg),	Intervention • EBR(50mg)/GZR(100mg)	Intervention • EBR(50mg)/GZR(100mg),	Intervention • EBR(50mg)/GZR(100mg) 12

Criteria	C-EDGE TN[18] NCT02105467	C-SURFER[20] NCT02092350	C-EDGE CO-STAR[59] NCT02105688	C-EDGE H2H[23] NCT02358044
details for administration, posology)	FDC tablet 12 weeks, taken once daily without regard to food Comparator • Placebo	FDC tablet • 12 weeks, taken once daily without regard to food Comparator • Placebo	FDC tablet 12 weeks Comparator • Placebo	weeks Comparator • SOF (400mg) once daily+P 1.5mcg per Kg once weekly, and RBV 1000-1200mg twice daily for 12 weeks
Concomitant medication	Concomitant medication† • Disallowed medication; known hepatotoxic drugs, herbal supplements, OATP inhibitors, HIV medicines, statins	Concomitant medication† • Allowed medication; anticoagulants, hypoglycemic agents, diuretics, hyperthyroidism. • Disallowed medication; known hepatotoxic drugs, herbal supplements, CYP3A/P-gp inhibitors, OATP inhibitors, HIV medicines, statins	Concomitant medication† • Allowed medication included; named anticoagulants, named antihypertensives, erythropoietin, diuretics, statins, hypoglycaemic agents, antidepressants. Disallowed medication; known hepatotoxic drugs, herbal supplements, strong and moderate CYP3A/p-gp inhibitors, named HIV medicine	Concomitant medication† • Disallowed medication included; hepatotoxic drugs, named herbal supplements, strong CYP3A/P-gp inducers, OATP inhibitors, and, named HIV medications.
Primary outcome (including scoring methods and timing of assessments)	Primary outcome • SVR12; blood test 12 weeks following the end of all treatment, using LLoQ <15 IU/mL • Safety and tolerability during therapy and follow-up	Primary outcome • SVR12; blood test 12 weeks following the end of all treatment, using LLoQ <15 IU/mL • Safety and tolerability during therapy and follow-up	Primary outcome • SVR12; blood test 12 weeks following end of treatment using LLoQ <15IU/mL • Safety and tolerability during therapy and follow-up	Primary outcomes • SVR12; blood test 12 weeks following end of treatment using LLoQ <15IU/mL • Safety and tolerability during therapy and follow-up
Secondary/other	Secondary objectives	Secondary objectives	Secondary objectives	Secondary objectives

Criteria	C-EDGE TN[18] NCT02105467	C-SURFER[20] NCT02092350	C-EDGE CO-STAR[59] NCT02105688	C-EDGE H2H[23] NCT02358044
objectives *Not reported in this submission*	• SVR 24 weeks <u>Other objectives</u> • Evaluate the efficacy of EBR/GZR by the proportion of patients in the immediate treatment arm achieving SVR24 • Evaluate the efficacy of EBR/GZR as assessed by the proportion of patients in the immediate treatment arm achieving undetectable HCV RNA and HCV RNA < LLoQ at Weeks 2, 4, 12 and Follow-Up week 4 (SVR4). • Describe and compare patient-reported outcomes related to HRQoL, fatigue, and work productivity/activity impairment before, during, and after treatment with EBR/GZR versus placebo. • Evaluate the emergence of RAVs to GZR or EBR when administered as part of a combination regimen. • Evaluate PK of EBR/GZR	• Analysis of RAVs among virological failures <u>Other objectives</u> • Evaluate the efficacy of EBR/GZR assessed by the proportion of patients achieving: • SVR24 HCV RNA <LLoQ (either TD(u) or TND) • SVR4 HCV RNA <LLoQ (either TD(u) or TND) • SVR 12 HCV RNA <LLoQ (either TD(u) or TND) for the deferred treatment arm • SVR12 HCV RNA <LLoQ (either TD(u) or TND) for all active and treatment arms combined • Evaluate the safety and tolerability of EBR/GZR for all treatment arms • Evaluate the emergence of RAVs to GZR or EBR • Evaluate PK of EBR/GZR • Evaluate PK/PD relationship EBR/GZR plasma levels in relation to efficacy and safety • Evaluate biomarkers that may	• Evaluate EBR/GZR assessed by proportion of patients in the immediate treatment arm achieving SVR24 • Evaluate EBR/GZR assessed by proportion of patients in the immediate treatment arm achieving undetectable HCV RNA <LLoQ at Weeks 2, 4 and 12 and Follow-Up Week 4 (SVR4). • Describe and compare patient reported outcomes related to HRQoL before, during, and after treatment with EBR/GZR vs. placebo • Evaluate the emergence of RAVs to GZR or EBR • Evaluate PK of EBR/GZR • In HIV co-infected patients only, evaluate proportion of patients who develop HIV-1 virological failure during protocol therapy • Evaluate effect of study regimen on CD4+ cell counts in HIV co-infected patients only.	• Evaluate safety profile of EBR/GZR as compared to SOF/PR as assessed by the proportion of patients experiencing a tier 1 safety event, defined as: ○ Any drug related SAE ○ any drug-related AE leading to permanent discontinuation of all study drugs ○ neutrophil count <0.75 × 109/L ○ haemoglobin <10 g/dL ○ any event leading to discontinuation of study drug • To evaluate whether EBR/GZR has superior efficacy to SOF/PR in the treatment of HCV, as assessed by the proportion of patients achieving SVR12, defined as HCV RNA < LLOQ (either TD[u] or TND) 12 weeks after the end of all study therapy <u>Other objectives</u> • Describe and compare patient reported outcomes related to HRQoL, fatigue, and

Criteria	C-EDGE TN[18] NCT02105467	C-SURFER[20] NCT02092350	C-EDGE CO-STAR[59] NCT02105688	C-EDGE H2H[23] NCT02358044
	• Explore relationship between genetic variation and patient response to treatment administered	be predictive of tolerability of study drugs and virologic response to EBR/GZR by comparing biomarker levels over time in patients who respond or fail study therapy. • describe and compare changes from baseline HRQoL during and after active and placebo treatment periods • Assess the genetic variation in the human IL28B gene as a predictor of virologic response in each treatment arm • Determine the impact of HCV treatment on cryoglobulinemia in patients with CKD		work productivity/activity impairment before, during, and after treatment with EBR/GZR+/- RBV vs. SOF/PR • Evaluate the efficacy of EBR/GZR and SOF/PR, as assessed by the proportion of patients achieving SVR24, defined as HCV RNA < LLOQ (either TD(u) or TND) 24 weeks after the end of all study therapy • Evaluate the efficacy of EBR/GZR and SOF/PR, as assessed by the proportion of patients achieving HCV RNA < LLOQ (either TND(u) or TND) at Week 2, 4, 12, and Follow-up Week 4 (SVR4). • Evaluate the efficacy of EBR/GZR and SOF/PR in subgroup populations. These subgroups include but are not limited to patients with cirrhosis, presence of IL-28 polymorphism, GT1b vs. non-1b, and higher baseline HCV RNA.

Criteria	C-EDGE TN[18] NCT02105467	C-SURFER[20] NCT02092350	C-EDGE CO-STAR[59] NCT02105688	C-EDGE H2H[23] NCT02358044
				• Evaluate the emergence of viral resistance-associated variants (RAVs) to EBR and/or GZR when administered as part of a combination regimen • Explore the relationship between genetic variation and response to the treatment(s) administered.
Post Hoc analysis	• SVR12 (GT1a, GT1b, GT4) split by cirrhosis stage in TN patients • Safety (GT1 or GT4) split by cirrhosis stage	• SVR12 (GT1a or GT1b) split by cirrhosis stage and treatment experience • Safety GT1 split by cirrhosis stage	• SVR12 (GT1a or GT1b) split by cirrhosis stage in treatment naïve patients • Safety GT1 split by cirrhosis stage	• SVR (GT1a, GT1b and GT4) split by cirrhosis stage and treatment experience • Safety GT1 and GT4 split by cirrhosis stage

Abbreviations: CSR, clinical study report; EBR/GZR, elbasvir/grazoprevir; HRQOL, health related quality of life; OATP, Organic Anion Transporting Polypeptide; LLOQ, Lower limit of quantification; mFAS, modified full analysis set; TBC, to be confirmed; P, pegylated-interferon alpha

† This is not an exhaustive list. Please see CS, Appendix 5 for full details for each study.

Table 4.6: Baseline characteristics for comparative EBR/GZR RCTs

	C-EDGE TN[18]		C-EDGE COSTAR[59]		C-SURFER[20]		C-EDGE H2H[23]	
	EBR/GZR 12 weeks N=316	**Placebo 12 weeks N=105**	**EBR/GZR 12 weeks N=201**	**Placebo 12 weeks N=100**	**EBR/GZR 12 weeks N=111**	**Placebo 12 weeks N=113**	**EBR/GZR 12 weeks N=129**	**SOF/PR 12 weeks N=126**
Age,								
Mean (SD)	52.2 (11.1)	53.8 (11.2)	47.4 (9.9)	46.4 (9.9)	56.5 (9.1)	55.2 (10.1)	47.6 (12.4)	48.2 (12.4)
Median (range)	54 (20-78)	55 (22-76)	48 (23-66)	47 (24-64)	-	-	49 (21-68)	49 (22-76)
Gender, n (%)								
Male	171 (54)	56 (53)	153 (76.1)	77 (77.0)	81 (73.0)	80 (70.8)	55 (42.6)	62 (49.2)
Female	145 (46)	49 (47)	48 (23.9)	23 (23.0)	30 (27.0)	33 (29.2)	74 (57.4)	64 (50.8)
Race, n (%)								
White	191 (60)	73 (70)	158 (78.6)	84 (84.0)	55 (49.5)	48 (42.5)	128 (99.2)	125 (99.2)
Black/African American	59 (19)	18 (17)	31 (15.4)	7 (7.0)	50 (45.0)	53 (46.9)	-	-
Asian	54 (17)	13 (12)	9 (4.5)	7 (7.0)	5 (4.5)	9 (8.0)	1 (0.8)	1 (0.8)
Other…	12 (4)	1 (1)	3 (1.5)	2 (2.0)	1 (0.9)	3 (2.7)	-	-
HCV genotype, n (%)								
GT1a	157 (50)	54 (51)	153 (76.1)	75 (75.0)	53 (47.7)	59 (52.2)	18 (14.0)	17 (13.5)
GT1b	131 (42)	40 (38)	30 (14.9)	15 (15.0)	58 (52.3)	53 (46.9)	105 (81.4)	104 (82.5)
GT4	18 (6)	8 (8)	12 (6.0)	6 (6.0)	-	-	6 (4.7)	5 (4.0)
GT6	10 (3)	3 (3)	5 (2.5)	4 (4.0)	-	-	-	-
IL28B CC genotype, n (%)	106 (34)	37 (35)	57 (28.4)	29 (29.0)	30 (27.0)	30 (26.5)	26 (20.2)	26 (20.6)
IL28B non-CC genotype, n (%)**	208 (66)	67 (64)	141 (70.1)	67 (67.0)	79 (71.2)	83 (73.5)	100 (77.5)	98 (77.8)
HCV baseline severity, n (%)								
≤ 800 000 IU/mL	94 (30)	39 (37)	-	-	50 (45.0)	47 (41.6)	39 (30.2)	45 (35.7)
> 800 000 IU/mL	222 (70)	66 (63)	-	-	61 (55.0)	66 (58.4)	90 (69.8)	81 (64.3)
Baseline HCV (log10 IU/ml),								
Mean (SD)	-	-	6.63 (6.74)	6.54 (6.63)	-	-	6.44 (6.50)	6.46 (6.75)

	C-EDGE TN[18]		C-EDGE COSTAR[59]		C-SURFER[20]		C-EDGE H2H[23]	
	EBR/GZR 12 weeks N=316	**Placebo 12 weeks N=105**	**EBR/GZR 12 weeks N=201**	**Placebo 12 weeks N=100**	**EBR/GZR 12 weeks N=111**	**Placebo 12 weeks N=113**	**EBR/GZR 12 weeks N=129**	**SOF/PR 12 weeks N=126**
Fibrosis status, n (%)[††]								
Cirrhotic	-	-	-	-	7 (6.2)	7 (6.2)	-	-
Non-cirrhotic	-	-	-	-	104 (93.7)	106 (93.8)	-	-
F0-F2	210 (67)	69 (66)	147 (73.1)	65 (65.0)	76 (68.5)	76 (67.3)	97 (75.2)	92 (73.0)
F3	36 (11)	14 (13)	14 (7.0)	13 (13.0)	13 (11.7)	15 (13.3)	9 (7.0)	13 (10.3)
F4	70 (22)	22 (21)	40 (19.9)	20 (20.0)	7 (6.3)	7 (6.2)	22 (17.1)	21 (16.7)
Other	-	-	-	-	15 (13.5)[†]	15 (13.3)[†]	-	-
Special populations, n (%)								
Opiate substitution therapy	-	-	201 (100)	100 (100)	-	-	-	-
CKD Stage 4	-	-	-	-	18 (16.2)	22 (19.5)	-	-
CKD Stage 5	-	-	-	-	93 (83.8)	91 (80.5)	-	-
On dialysis	-	-	-	-	86 (77.5)	87 (77.0)	-	-
Not on dialysis	-	-	-	-	25 (22.5)	26 (23.0)	-	-
Diabetes	-	-	-	-	38 (34.2)	36 (31.9)	-	-
No diabetes	-	-	-	-	73 (65.8)	77 (68.1)	-	-
Treatment history, n (%)								
Naïve	316 (100)	105 (100)	201 (100)	100 (100)	91 (82.0)	88 (77.9)	100 (77.5)	91 (72.2)
Experienced	-	-	-	-	20 (18.0)	25 (22.1)	29 (22.5)	35 (27.8)
Previous virological response, n (%)								
PR Null response	-	-	-	-	-	-	11 (8.5)	14 (11.1)
PR Partial response	-	-	-	-	-	-	6 (4.7)	8 (6.3)
PR Relapser	-	-	-	-	-	-	12 (9.3)	13 (10.3)

Abbreviation: CKD, chronic kidney disease; DAA, direct acting antiviral; EBR/GZR, grazoprevir/elbasvir; HCV, hepatitis C virus; IFN, interferon; PR, pegylated-interferon alpha in combination with ribavirin.

[†]Other category applies to 30 patients assessed by Fibrotest but could not be considered cirrhotic; **3 patients in the EBR/GZR arm (C-EDGE H2H) had IL28B GT data missing, and 2 patients in the SOF/PR arm had IL28B GT data missing; [††] 1 patient in the EBR/GZR treatment arm (C-EDGE H2H) did not have a fibrosis stage score

4.2.1 Results

The CS reports clinical effectiveness results according to the primary objective (SVR12) for each of the included EBR/GZR RCTs (n=7) as relevant to the anticipated EMA label and the context of this submission, i.e. the treatment of patients with chronic HCV GT1a, GT1b, and GT4 infections treated with EBR/GZR for 12 weeks split according to treatment experience and cirrhosis stage, where available from the CSR. Here we will only report results for the RCT that include a relevant comparator: C-EDGE H2H, comparing EBR/GZR with SOF/PR for 12 weeks. The other trials either compared EBR/GZR with placebo (resulting in 0% SVR12) or with less relevant treatment regimes such as EBR/GZR/RBV or EBR/GZR for 16 weeks. Results of the placebo controlled randomised trials in terms of adverse events will be reported below.

C-EDGE H2H[23]

A total of 255 patients were randomised to EBR/GZR or SOF/PR for 12 weeks. The primary endpoint, SVR12, was reported using the FAS population. For patients with Gt1 and GT4, SVR12 was 99.2% (n=128/129) and 90.5% (n=114/126) for the EBR/GZR and SOF+PR treatment arms, respectively. The estimated adjusted difference between the two treatment groups was 8.8% (95% CI, 3.6%, 15.3%). As the lower bound of the one-sided one-sample exact test was greater than -10%, the non-inferiority of EBR/GZR compared with SOF+PR was established. The efficacy estimates for EBR/GZR and SOF+PR were comparable among GT1a infected patients, whereas the observed efficacy of EBR/GZR was higher than SOF+PR in patients with GT1b infection; these values are summarised in Table 4.7.

Table 4.7: SVR12 results for patients treated with EBR/GZR or SOF+PR for 12 weeks

Treatment arm	EBR/GZR, 12 weeks		SOF+PR, 12 weeks		Unadjusted difference in %
	n/N	%	n/N	%	
GT1 and 4	128/129	99.2	114/126	90.5	8.7[†]
GT1a	18/18	100	17/17	100	0.0 (-18.0, 18.9)
GT1b	104/105	99	94/104	90.4	8.7 (3.2, 16.0)
GT4	6/6	100	3/5	60	40 (-10.9, 78.1)

Abbreviations: FAS, full analysis set, EBR/GZR, grazoprevir/elbasvir; SOF+PR, sofosbuvir/peg-IFN+RBV; SVR, sustained virologic response

[†] P<0.001

4.2.2 Adverse events

C-EDGE TN[18]

A total of 421 patients were randomised to EBR/GZR (n=316) or placebo (n=105) for 12 weeks. Overall, adverse events (AEs) occurred in 67.4% (n=213/316) and 68.6% (n=72/105) at a frequency of ≥5% in patients in the immediate and placebo group, respectively. Drug related AEs, as determined by the investigator, occurred in 36.1% (n=114/316) and 39% (n=41/105) of patients in the active and placebo group, respectively; with a difference of -2.9% (95% CI, -13.7 to 7.5). The most commonly reported AEs were headache (16.5%), fatigue (15.5%), and nausea (8.9%); this was comparable in both the immediate and placebo treatment group. Serious AEs during treatment and within the first 14 follow-up days were reported in 2.8% (n=9/316) and 2.9% (n=3/105) of patients in the active and

placebo groups, respectively; none of which were considered to be study drug related. Two deaths in the immediate treatment group were observed, but not considered study drug related. In total four patients discontinued therapy. Three of the four patients were randomised to the immediate treatment arm and discontinued treatment due to elevated transaminase to >5x ULN (n=2), and palpitations/anxiety (n=1). A single patient randomised to the placebo group discontinued related to a rash on day two of therapy.

The table below summarises safety events for patients randomly assigned to immediate or deferred therapy with EBR/GZR (initial treatment period and first 14 days after completion of treatment).

Table 4.8: C-EDGE TN: Tabulated summary of AEs for study C-EDGE TN

	GZR/EBR, n (%) N=316	**Placebo, n (%) N=105**
AE occurring in ≥5% of patients*		
≥1 AE	213 (67.4)	72 (68.6)
Headache	52 (16.5)	19 (18.1)
Fatigue	49 (15.5)	18 (17.1)
Nausea	28 (8.9)	7 (7.6)
Drug-related AE	114 (36.1)	41 (39)
Serious adverse events[†]		
≥1 SAE	9 (2.8)	3 (2.9)
Discontinuation		
Discontinued due to AE	3 (0.9)	1 (1)
Discontinuation due to drug-related AE¶	2 (0.6)	1 (1)
Discontinued due to SAE	0 (0)	0 (0)
Discontinuation due to drug-related SAE	0 (0)	0 (0)
Alanine aminotransferase[§]		
1·1–2·5 × baseline	9 (4)	58 (55)
>2·5 × baseline	2 (06)	2 (2)
>5·0 × baseline	3 (0.9)	0 (0)
Aspartate aminotransferase[§]		
1·1–2·5 × baseline	9 (4)	49 (47)
>2·5 × baseline	4 (1)	2 (2)
>5·0 × baseline	1 (0.3)	0 (0)
Elevation of bilirubin		
>2·5–5·0 × baseline	3 (0.9)	0 (0)
>5·0–10·0 × baseline	1 (0.3)	0 (0)
>10·0 × baseline	0 (0)	0 (0)

Abbreviations: AE, adverse events, GZR/EBR, grazoprevir/ elbasvir; SAE, serious adverse event

* Common adverse events occurring in at least 5% of patients in either treatment arm during the immediate treatment period or the first 14 days of follow-up.

[†]Four patients in the immediate-treatment group had serious adverse events (none were considered drug-related) after the first 14 days of follow-up, which included tooth abscess (2 months, 7 days since last dose), chest pain (1 month, 27 days since last dose), asthenia/hypotension/ acute pancreatitis (3 months, 1 day to 3 months, 17 days since last dose), and pancreatic mass (4 months, 1 day since last dose).

[¶] Study medication withdrawn

[§]No ALT or AST elevations were associated with elevations in total bilirubin

C-EDGE CO-STAR[59]

A total of 421 patients were randomised to EBR/GZR (n=316) or placebo (n=105) for 12 weeks. The most commonly reported AEs, reported in more than 10% of patients, with similar frequency across treatment arms were; fatigue (15.9%), headache (12.4%), and nausea (10.9%). Overall, one or more AEs were reported in 82.6% (n=166/201) and 83% (n=83/100) of patients in the immediate or deferred treatment groups, respectively. The authors of the CSR comment that the AEs reported in C-CO-STAR are similar to those reported for other EBR/GZR trials, indicating that the concomitant use of OST as well as other illicit drug use did not affect the overall safety profile of the regimen.

Drug related AEs were reported in 41.3% (n=83/201) and 34% (n=34/100) of patients in the active and deferred (placebo) group during initial blinded therapy, respectively. Serious AEs were reported in 3.5% (n=7/201) and 4.0% (n=4/100) patients in the immediate and deferred treatment groups, respectively. Of note, a single patient in the immediate treatment arm reported a serious drug-related AE; this was reported as "worsening auditory hallucinations". However, this patient achieved SVR12. One patient in the deferred (placebo) group experienced a serious drug-related AE, discontinued medication, and died related to acute respiratory distress syndrome; this was not considered to be related to study drug. Two patients (one patient in each treatment arm during blinded therapy) discontinued study medication as a result of AEs.

A summary of safety events reported for patients in the immediate and deferred (placebo) treatment groups (initial treatment period and first 14 days after completion of treatment) is reported below.

Table 4.9: Tabulated summary of AEs for study C-EDGE CO-STAR

	GZR/EBR, n (%) N=201	**Placebo, n (%) N=100**
Drug related AE[†]	83 (41.3)	34 (34.0)
Serious AE	7 (3.5)	4 (4.0)
Drug-related serious adverse event[†]	1 (0.5)	1 (1.0)
Discontinuation due to an adverse event	1 (0.5)	1 (1.0)
Discontinued due to a drug related AE[†]	1 (0.5)	0
Discontinued due to a serious AE	0	1 (1.0)
Discontinued due to a drug related SAE[†]	0	0
Deaths	0	1 (1.0)
AE occurring in >10% in any treatment group*		
≥1 AE	166 (82.6)	83 (83.0)
Gastrointestinal disorders	78 (38.8)	37 (37.0)
Nausea	22 (10.9)	9 (9.0)
Fatigue	32 (15.9)	20 (20.0)
Infections and infestations	44 (21.9)	29 (29.0)
Headache	25 (12.4)	13 (13.0)
Psychiatric disorders	44 (21.9)	25 (25.0)
Skin and subcutaneous tissue disorders	18 (9.0)	14 (14.0)

Abbreviation: AE, adverse event; GZR/EBR, grazoprevir/ elbasvir; SAE, serious adverse event
[†]Determined by the investigator to be study drug related
*Incidence 10% or more in one or more treatment groups during the initial treatment period and for 14 days after the completion of treatment (all patients as treated)

C-SURFER[20]

A total of 237 (11 received open label intensive pharmacokinetic EBR/GZR) patients were randomised to EBR/GZR (n=112) or placebo (n=114) for 12 weeks.

The frequency of AEs was comparable between the immediate and deferred treatment groups at 75.7% and 84.1%, respectively. Most AEs were considered to be mild or moderate, irrespective of treatment group. The most common AEs (≥10% frequency) were headache (17.1%), nausea (15.3%), and fatigue (9.9%); these were comparable in the two groups (summarised in the Table below). A total of 16 (14%) patients in the immediate treatment group and 19 (17%) patients in the deferred treatment group reported a serious AE during treatment or within 14 days after the end of treatment. Two cases of congestive heart failure occurred in the immediate treatment group within 14 days of the end of treatment; one of these, judged by the investigator to be drug-related, was reported six weeks after study treatment ended. The authors commented that the SAE reported were consistent with the underlying co-morbidities and complications within this patient population.

There were four deaths, none considered related to study drug, during the initial treatment period plus 14 days. One patient in the immediate treatment group died from cardiac arrest, and three patients in the deferred treatment group died from aortic aneurysm, pneumonia, and an unknown cause of death. There were no discontinuations related to AEs in the immediate treatment group versus five patients in the deferred treatment group.

Summarised in the table below are safety events reported for the immediate and deferred treatment groups (initial treatment period and first 14 days after completion of treatment)

Table 4.10: Tabulated summary of AEs for study C-SURFER

	GZR/ EBR, n (%) N=111	**Placebo (%) N=113**
Any adverse event*†	84 (75.7)	95 (84.1)
Headache	19 (17.1)	19 (16.8)
Nausea	17 (15.3)	18 (15.9)
Fatigue	11 (9.9)	17 (15.0)
Insomnia	7 (6.3)	12 (10.6)
Dizziness	6 (5.4)	18 (15.9)
Diarrhoea	6 (5.4)	15 (13.3)
Drug related AE†	38 (34.2)	39 (34.5)
Serious AE†	16 (14.4)	19 (16.8)
Drug-related serious adverse event†	0	1 (0.9)
Discontinuation due to an adverse event	0	5‡ (4.4)
Deaths	1 (0.8)	3 (2.7)
Lowest haemoglobin on treatment§		
8·5–10·0 g/dL	27 (24.3)	19 (16.8)
<8·5 g/dL	5 (4.5)	5 (4.4)
Alanine aminotransferase§		
1·1–2·5 × baseline	2 (1.8)	36 (31.9)
>2·5 × baseline	1 (0.8)	6 (5.3)

>5·0 × baseline	0	1 (0.9)
Aspartate aminotransferase[§]		
1·1–2·5 × baseline	4 (3.6)	38 (33.6)
>2·5 × baseline	0	4 (4.6)
>5·0 × baseline	0	0
Bilirubin[§]		
>2·5–5·0 × baseline	1 (0.9)	3 (2.7)
>5·0–10·0 × baseline	0	0
>10·0 × baseline	0	0
Alkaline phosphatase[§]		
1·1–2·5 × baseline	42 (37.8)	36 (31.9)
>2·5 × baseline	0	0
>5·0 × baseline	0	0
Creatinine >2·5 × baseline	1 (1.2)	0
Change in blood urea nitrogen (mg/L) from baseline at treatment week 12[§¶]	-1.5 (3.6)	0.9 (2.6)

* Incidence 10% or more in one or more treatment groups during the initial treatment period and for 14 days after the completion of treatment (all patients as treated)
†Number of patients with the specific adverse event.
‡Abdominal pain, elevated alanine transaminase and aspartate transaminase, acute myocardial infarction, atrial fibrillation with myocardial infarction, and increased lipase.
§Data presented for patients with more than 1·0 change from baseline.
¶Patients not on dialysis at baseline (immediate treatment group, n=25; deferred treatment group, n=24).

C-EDGE H2H[23]

A total of 255 patients were randomised to EBR/GZR or SOF/PR for 12 weeks.

The authors of the CSR reported that the safety profile for "tier 1" events for EBR/GZR compared with SOF/PR was statistically significantly better (the authors reporter superiority for EBR/GZR) with a between difference of -27% (95% CI -35.5 to -19.6) p<0.001 (see also Table below). Tier 1 events included but were not limited to: any serious drug related event including, any AE, or any drug related AE leading to permanent discontinuation of all study drugs.

The proportion of patients experiencing an AE or drug related AE in the SOF/PR group was higher compared with EBR/GZR. In addition, only headache was reported at a frequency of >10% in patients randomised to EBR/GZR compared with patients in the SOF/PR arm who reported a events with a frequency of >10% for: pyrexia, headache, fatigue, asthenia, influenza-like illness, chills, myalgia, decreased appetite, anaemia, nausea, and cough. Similarly, the frequency of SAEs and drug related SAEs was higher in the SOF/PR arm vs. EBR/GZR.

Summarised in the table below are safety events reported in the EBR/GZR and SOF/PR treatment arms (initial treatment period and first 14 days after completion of treatment).

Table 4.11: Tabulated summary of AEs for study C-EDGE H2H

	EBR/GZR 12 weeks N=129	SOF/PR 12 weeks N=126
AE occurring in >10% in any treatment group		
≥1 AE	67 (51.9)	117 (92.9)
Anaemia	1 (0.8)	16 (12.7)
Nausea	8 (6.2)	13 (10.3)
Fatigue	9 (7.0)	32 (25.4)
Asthenia	7 (5.4)	30 (23.8)
Chills	2 (1.6)	21 (16.7)
Influenza like illness	1 (0.8)	23 (18.3)
Pyrexia	2 (1.6)	68 (54.0)
Infections/ infestations	11 (8.5)	33 (26.2)
Myalgia	4 (3.1)	19 (15.1)
Arthralgia	4 (3.1)	13 (10.3)
Headache	17 (13.2)	50 (39.7)
Psychiatric disorders	6 (4.7)	32 (25.4)
Gastrointestinal disorders	27 (20.9)	104 (82.5)
Tier 1 Adverse events	1 (0.8)	35 (27.8)
Drug-related AE	32 (24.8)	114 (90.5)
SAE overall	1 (0.8)	5 (4.0)
SAE study drug related	0 (0.0)	3 (2.4)
Tier 1 Adverse events	1 (0.8)	35 (27.8)
Discontinuation		
Discontinued* due to AE	0 (0.0)	1 (0.8)
Discontinued* due to drug related AE	0 (0.0)	1 (0.8)
Discontinued* due to SAE	0 (0.0)	0 (0.0)
Discontinued* due to drug related SAE	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse events, GZR/EBR, grazoprevir/ elbasvir; SOF/PR, sofosbuvir + PEG-INF + RBV
*Determined by the investigator to be study drug related

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As described in Section 4.1.2 of this report, 50 publications, representing 40 clinical trials were included in the CS; 15 of these publications, representing eight clinical trials involved EBR/GZR.

However, only four studies evaluating EBR/GZR for 12 weeks included a relevant control arm (3x placebo and one SOF/PR). In addition, only 25 out of 32 comparator studies are RCTs. Therefore, only 29 out of the 40 trials are appropriate for a proper NMA.

The company included 40 trials in the NMA (using either single arms or imputed study arms), grouped by primary intervention giving eight for EBR/GZR, five for SMV/PR, five for SOF/PR, eight for 3D and/or 3D/RBV, one for 2D/RBV, nine for LDV/SOF, two for DCV/SOF, one for DCV/PR,

and finally one for TVR/PR that was included to increase the robustness of the network according to the company. Most trials were included in both the analysis of SVR and safety, with the exception of ATOMIC, AI444040, ERADICATE, and LONESTAR which only featured in the safety analysis, and ALLY-2 which was only analysed for SVR.

The trials included in each analysis by treatment group and drug are summarised in Tables 4.12 to 4.14.

Table 4.12: GT1a/GT1b trials of included interventions for the NMA of SVRs

	Genotype 1a			
	Treatment-naïve		**Treatment experienced**	
	Cirrhosis	**No cirrhosis**	**Cirrhosis**	**No cirrhosis**
Comparator	**Trials**	**Trials**	**Trials**	**Trials**
EBR/GZR 1-12[60]	C-EDGE TN[18], C-EDGE CO-INFECTION[58], C-SURFER[20], C-WORTHY[21], C-EDGE CO-STAR[59]	C-EDGE TN[18], C-EDGE CO-INFECTION[58], C-SURFER[20], C-WORTHY[21], C-EDGE CO-STAR[59], PN077[23]	C-EDGE TE[19], C-SURFER[20], C-WORTHY[21]	C-EDGE TE[19], C-SURFER[20], C-WORTHY[21], PN077[23]
PR 1-48	QUEST-1[42], QUEST-2[43]	ADVANCE[24], PILLAR[40], QUEST-1[42], QUEST-2[43]	PROMISE[41]	PROMISE[41]
SOF/PR 1-12	Pearlman et al., 2015[39]	PN077[23], Rodriguez-Torres et al., 2015[55]	Pearlman et al., 2015[39]	PN077[23], Pol et al., 2015[54]
SMV/PR 1-12, PR 13-24	QUEST-1[42], QUEST-2[43]	PILLAR[40], QUEST-1[42], QUEST-2[43]	PROMISE[41]	PROMISE[41]
3D/RBV 1-12	Not recommended by NICE	MALACHITE-I[34], PEARL-IV[38], SAPPHIRE-I[44]	Not recommended by NICE	MALACHITE-II[34], SAPPHIRE-II[45]
3D/RBV 1-24	TURQUOISE-II[46]	Not recommended by NICE	TURQUOISE-II[46]	Not recommended by NICE
LDV/SOF 1-8	Not recommended by NICE	ION-3[32]	Not recommended by NICE	Not recommended by NICE
LDV/SOF 1-12	ION-1[30], Lim et al., 2015[52], Mizokami et al., 2015[35], SYNERGY[50, 61-63]	Not recommended by NICE	ELECTRON[29], ION-2[31], Lim et al., 2015[52], Mizokami et al., 2015[35]	ION-2[31], Lim et al., 2015[52], Mizokami et al., 2015[35], SYNERGY[50, 61-63]
DCV/SOF 1-12	Not recommended by NICE	ALLY-2[26]	Not recommended by NICE	ALLY-2[26]
	Genotype 1b			
	Treatment-naïve		**Treatment experienced**	
	Cirrhosis	**No cirrhosis**	**Cirrhosis**	**No cirrhosis**
Comparator	**Trials**	**Trials**	**Trials**	**Trials**
EBR/GZR1-12[26]	C-EDGE TN[18], C-EDGE CO-INFECTION[58], C-WORTHY[21], C-EDGE CO-STAR[59], PN077[23]	C-EDGE TN[18], C-EDGE CO-INFECTION[58], C-SURFER[20], C-WORTHY[21], C-EDGE CO-STAR[59], PN077[23]	C-EDGE TE[19], C-WORTHY[21], PN077[23]	C-EDGE TE[19], C-SURFER[20], C-WORTHY[21], PN077[23]

PR 1-48	QUEST-1[42], QUEST-2[43]	ADVANCE[24], PILLAR[40], QUEST-1[42], QUEST-2[43]	PROMISE[41]	PROMISE[41]
SOF/PR 1-12	PN077[23]	PN077[23], Rodriguez-Torres et al., 2015[55]	PN077[23]	PN077[23], Pol et al., 2015[54]
SMV/PR 1-12, PR 13-24	QUEST-1[42], QUEST-2[43]	PILLAR[40], QUEST-1[42], QUEST-2[43]	PROMISE[41]	PROMISE[41]
3D/RBV 1-12	TURQUOISE-II[46]	Not recommended by NICE	TURQUOISE-II[46]	Not recommended by NICE
3D 1-12	Not recommended by NICE	MALACHITE-I[34], PEARL-IV[38]	Not recommended by NICE	PEARL-II[37]
LDV/SOF 1-8	Not recommended by NICE	ION-3[32]	Not recommended by NICE	Not recommended by NICE
LDV/SOF 1-12	ION-1[30], Lim et al., 2015[52], Mizokami et al., 2015[35], SYNERGY[50, 61-63]	Not recommended by NICE	ELECTRON[29], ION-2[31], Lim et al., 2015[52], Mizokami et al., 2015[35]	ION-2[31], Lim et al., 2015[52], Mizokami et al., 2015[35], SYNERGY[50, 61-63]
DCV/SOF 1-12	Not recommended by NICE	ALLY-2[26]	Not recommended by NICE	ALLY-2[26]

Source: CS, Table 35, page 124.

Abbreviations: DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, pegylated-interferon and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

Table 4.13: GT4 trials of included interventions for the NMA of SVRs

	Genotype 4			
	Treatment-naïve		Treatment experienced	
	Cirrhosis	No cirrhosis	Cirrhosis	No cirrhosis
Comparator	**Trials**	**Trials**	**Trials**	**Trials**
EBR/GZR 1-12[60]	C-EDGE TN[18], C-EDGE CO-INFECTION[58], PN077[23]	C-EDGE TN[18], C-EDGE CO-INFECTION[58], C-SCAPE[47], PN077[23]	C-EDGE TE[19], PN077[23]	C-EDGE TE[19], PN077[23]
PR 1-48	COMMAND-4[28]	COMMAND-4[28]	COMMAND-4[28]	COMMAND-4[28]
SOF/PR 1-12	NEUTRINO[53], Pearlman et al., 2015[39], PN077[23]	Not recommended by NICE	Pearlman et al., 2015[39], PN077[23]	Not recommended by NICE
SMV/PR 1-12, PR 13-24	RESTORE[49]	RESTORE[49]	RESTORE[49]	RESTORE[49]
2D/RBV 1-12	Not recommended by NICE	PEARL-I[36, 64]	Not recommended by NICE	PEARL-I[36, 64]
2D/RBV 1-24	PEARL-I[36, 64]	Not recommended by NICE	PEARL-I[36, 64]	Not recommended by NICE
LDV/SOF 1-8	Not recommended by NICE			
LDV/SOF 1-12	ION-1[30], Lim et al., 2015[52], Mizokami et al., 2015[35], SYNERGY[50, 61-63]	Not recommended by NICE	ELECTRON[29], ION-2[31], Lim et al., 2015[52], Mizokami et al., 2015[35]	ION-2[31], Lim et al., 2015[52], Mizokami et al., 2015[35], SYNERGY[50, 61-63]
DCV/SOF 1-12	Not recommended by NICE	Not recommended by NICE	Not recommended by NICE	ALLY-2[26]
DCV/PR 1-24	COMMAND-4[28]	COMMAND-4[28]	COMMAND-4[28]	COMMAND-4[28]

Source: CS, Table 36, page 125.

Abbreviations: DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, pegylated-interferon alpha and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

Table 4.14: GT1/GT4 trials of included intervention for the NMA of safety outcomes

	Genotype 1		Genotype 4	
	Cirrhosis	No cirrhosis	Cirrhosis	No cirrhosis
Comparator	Trials	Trials	Trials	Trials
EBR/GZR1-12	C-EDGE TN[18], C-EDGE TE[19], C-EDGE CO-INFECTION[58], C-SURFER[20], C-WORTHY[21], C-EDGE CO-STAR[59], PN077[23]	C-EDGE TN[18], C-EDGE TE[19], C-EDGE CO-INFECTION[58], C-SURFER[20], C-WORTHY[21], C-EDGE CO-STAR[59], PN077[23]	C-EDGE TN[18], C-EDGE TE[19], C-EDGE CO-INFECTION[58]	C-EDGE TN[18], C-EDGE TE[19], C-EDGE CO-INFECTION[58], C-SCAPE[47], PN077[23]
PR 1-48	PROMISE[41], QUEST-1 [42], QUEST-2[43]	PILLAR[40]	COMMAND-4[28]	COMMAND-4[28]
SOF/PR 1-12	Pearlman et al., 2015 [39], PN077[23]	ATOMIC[27], Pol et al., 2015 [54], PN077[23]	Pearlman et al., 2015 [39], PN077[23]	Not recommended by NICE
SMV/PR 1-12, PR 13-24	PROMISE[41], QUEST-1 [42], QUEST-2[43]	PILLAR[40]	RESTORE[49]	RESTORE[49]
2D 1-12	Not recommended by NICE	MALACHITE-I[34], PEARL-II[37], PEARL-III[38], PEARL-IV[38]	Not recommended by NICE	Not recommended by NICE
3D/RBV 1-12	TURQUOISE-II[46]	MALACHITE-I[34], MALACHITE-II[34], PEARL-II[37], PEARL-III[38], PEARL-IV[38], SAPPHIRE-I,[44] SAPPHIRE-II[45]	Not recommended by NICE	Not recommended by NICE
3D/RBV 1-24	TURQUOISE-II[46]	Not recommended by NICE	Not recommended by NICE	Not recommended by NICE
2D/RBV 1-12	Not recommended by NICE	Not recommended by NICE	Not recommended by NICE	PEARL-I[36, 64]
2D/RBV 1-24	Not recommended by NICE	Not recommended by NICE	PEARL-I[36, 64]	Not recommended by NICE
LDV/SOF 1-8	Not recommended by NICE	ION-3[32], LONESTAR[33]	Not recommended by NICE	Not recommended by NICE
LDV/SOF 1-12	ELECTRON[29], ION-1[30], ION-2[31], Lim et al., 2015[52], L LONESTAR[33], Mizokami et al., 2015[35], SYNERGY[50, 61-63]	ERADICATE[48], ION-3[32], LONESTAR[33], SYNERGY[50, 61-63]	ELECTRON[29], ION-1[30], ION-2[31], Lim et al., 2015[52], L LONESTAR[33], Mizokami et al., 2015[35], SYNERGY[50, 61-63]	ERADICATE[48], ION-3[32], LONESTAR[33], SYNERGY[50, 61-63]
DCV/SOF 1-12	Not recommended by NICE	AI444040[28]	Not recommended by NICE	AI444040[28]
DCV/PR 1-24	Not recommended by NICE	Not recommended by NICE	COMMAND-4[28]	COMMAND-4[28]

Source: CS, Table 37, page 126.

Abbreviations: DCV, daclatasvir; DAS, dasabuvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; PAR/r, paritaprevir/ritonavir; PR, pegylated-interferon alpha and ribavirin; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

ERG comment: In general the ERG agrees with including RCTs as identified and as listed in Table 4.2. The first 31 trials listed in Table 4.2 are relevant trials and most of these include relevant comparators. With these studies it might have been possible to perform a proper network meta-analyses for patients with GT1 and either split by treatment experience or cirrhosis status. However, by splitting the population by type of GT1 (1a and 1b), by treatment experience and by cirrhosis status, it is no longer possible to create a linked network.

The ERG does not believe that combining single arms from studies is a valid and reliable synthesis of available evidence.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company states that the NMA was designed to provide comparative estimates for EBR/GZR vs. other interventions currently recommended by NICE for patients with HCV for the following outcomes:

1. SVR, defined as the proportion of patients with HCV RNA less than the lower limit of quantification either 12 or 24 weeks after completion of treatment
2. Discontinuation related to AEs (DAE), defined as the proportion of patients who permanently discontinue all study drugs prior to completion of treatment
3. Overall AEs (OAE), defined as the proportion of patients experiencing any type of AE up to 30 days post treatment
4. Anaemia, nausea, neutropenia, pruritus, and rash, defined for each outcome as the proportion of patients experiencing an event up to 30 days post treatment.

The NMA of SVR was carried out across 12 different subgroups, each representing a different GT or sub-GT, prior treatment history, and cirrhosis status.

The company used two techniques to measure treatment comparisons across trials:

- Naïve comparisons: Individual arms of included studies were pooled and compared directly with each other.
- NMA with imputed control arms: for each non-comparative trial, an imputed PR control arm was created, estimated from the PR arms of comparative trials. A connected network of evidence was thus developed where the non-comparative trials connect through their imputed PR arms allowing NMA to be performed.

ERG comment: The naïve comparison comprised of two stages:

1. Pooling results from all the study arms of a particular treatment. This was done by adding all the data, so the numerator was the sum of the events and the denominator was the sum of the number of patients. This is not strictly a meta-analysis as it ignores differences in the sizes of the studies and treats them all equally in the pooled result. If the data had been combined using a meta-analysis then some form of weighting would have been used so the results from larger studies were given more weight in the analysis.
2. The pooled proportions were then compared between treatment regiments by calculating the differences (proportion A – proportion B) and relative risks (RR proportion A/proportion B).

Calculating the RR based on pooled proportions in this way is incorrect as it is ignoring the randomisation within the trials. This was highlighted in the submission which says “This is the least robust method of comparing treatments across trials”. All methods of meta-analysis, whether a direct

comparison between two treatments or indirect or network meta-analysis methods comparing two treatments which although not directly compared can be linked through a common control treatment, are based on the randomised treatment effect. This is the difference between the randomised treatments within each trial, in this case based on the proportions of patients with an event. Methods of meta-analysis should respect randomisation, so breaking randomisation by using single arms from different trials is not an appropriate approach and also ignores possible heterogeneity between the trials in terms of populations, settings, treatments and timings and methods of outcome measurement.

The NMA included non-comparative trials by imputing data for the relevant control arms (creating new data for arms that did not actually exist within the trial). The pegylated-interferon alpha in combination with ribavirin (PR) arms in the included trials were used for the imputation by forming a logistic regression model to estimate a weighted proportion for the PR arms. This value (e.g. 0.5) was then used to estimate the numbers of patients with an event and the denominator for each of the trials that were missing a PR arm. The sample sizes in existing trial arms were then reduced to avoid artificially increasing precision by preserving the probability of the event to ensure that "the estimation intervals do not become narrower based on the addition of data that were never observed" (CS, Appendix 8).

"The NMAs were performed in the Bayesian framework. Both fixed and random effects NMA were conducted for all outcomes and subgroups, with results presented as relative risks (RRs). RRs were selected over odds ratios as they were expected to be more stable as well as being more readily interpretable. For both fixed and random effects models, the goodness-of-fit of model predictions to the observed data was measured by calculating the posterior mean residual deviance." (CS, Appendix 8). The company presented both fixed and random effects model results rather than choosing between them based on model fit. This was appropriate and the choice of model had little impact on the results and conclusions. RRs are more easily interpretable than odds ratios but they are not likely to be more stable in the analysis as that is modelling the log odds of the event within each trial, not the risks. The RR then has to be calculated from the model results, it does not form part of the analysis.

There are a number of underlying assumptions which need to be considered when performing a NMA. The first of which is whether there is actually a network of trial evidence. To compare a set of treatments using RCT evidence there needs to be a network of trials which are connected by one or more common comparators (e.g. placebo as if you have treatment A compared to placebo and treatment B compared to placebo, then you can use their results to indirectly compare treatment A with treatment B using the randomised treatment effect). If you don't have a connected network then you cannot perform a NMA. None of the trial networks presented were connected so NMA methods were not appropriate, as they could only be performed by inventing trial arms which did not really exist. The submission says that:

"The use of traditional NMA hinges on two conditions. The first is consistency of direct and indirect evidence within closed loops. The second is that the network must be connected. The second condition is not met in this evidence base for multiple comparators. For example, SOF + LDV and DCV + SOF have not been featured in any head-to-head trials, and only OMB + PAR/r + DAS ± R 1-12 of the 3D/2D regimens has been compared directly with another comparator (TVR)." (CS, Appendix 8).

However, there are more than two underlying conditions, clinical and statistical heterogeneity between the trials should also be addressed, which have not been considered in the submission. The connectedness of the network should really be the first condition as without that there is no need to consider any other conditions such as the consistency of direct and indirect evidence within closed loops. As recognised in the submission the networks were not connected which means that a traditional NMA was not possible.

The main concern is that within some of the NMA analyses, most of the PR data were imputed, not just for a few trials. For example, the SVR analysis in genotype 1a patients who were treatment-naïve, without cirrhosis. This includes 17 trials, only four of which contain a PR arm, the other 13 (76%) have had PR data imputed so they can be included in the analysis. The imputed PR data used a proportion of 0.5 based on a pooled proportion from the four existing trials. However the same value was used for every imputation, when in reality the proportions ranged from 0.44 to 0.66 across the trials. Sensitivity analyses using other values would have been valuable, or using multiple imputation methods (with random sampling of possible values). Using the same imputed proportion across all trials means that there was less variation between the trial results than would be seen if they did actually contain a PR arm. This means that the SD is likely to be smaller resulting in a narrower credible interval which is more likely to show results favouring treatment. The use of single value imputation does not reflect differences between the trials in terms of their populations and methods, and means that the results may show statistically meaningful differences which do not really exist.

The results from the naïve and NMA analyses were very similar, which would be expected given that they are both using the same pooled proportion for the PR control arms.

4.4.1 SVR results from the NMA

The company states that the naïve comparison is the least robust method of comparing treatments across trials; therefore, we will only report the results from the NMA with imputed data here. However it should also be noted that there are also serious limitations with the NMA results due to the lack of connected trial networks and the imputation of missing treatment arms.

Table 4.15: NMA SVR results (random effects) for GT1a patients (RR (95% CrI))

Comparison EBR/GZR 1-12 vs.	GT1a TN NC patients	GT1a TN C patients	GT1a TE NC patients	GT1a TE C patients
PR 1-48	**1.86 (1.70, 2.03)**	**2.68 (2.00, 3.80)**	**2.28 (1.68, 2.95)**	**4.03 (2.23, 6.79)**
SMV/PR 1-12, PR 13-24 or PR 13-48	**1.20 (1.09, 1.42)**	**1.50 (1.06, 3.90)**	1.13 (0.87, 2.55)	1.30 (0.79, 17.76)
SOF/PR 1-12	1.05 (0.95, 1.46)	1.18 (0.96, 7.19)	1.12 (0.86, 2.17)	1.33 (0.77, 26.22)
LDV/SOF 1-8/12	1.01 (0.95, 1.16)	1.00 (0.92, 1.11)	0.96 (0.76, 1.04)	0.99 (0.63, 1.22)
3D/RBV 1-12/24	0.98 (0.93, 1.03)	1.04 (0.94, 1.78)	0.96 (0.76, 1.07)	1.00 (0.66, 3.14)
DCV/SOF 1-12	0.98 (0.93, 1.13)	--	0.97 (0.77, 1.37)	--

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00).
Abbreviations. C, with cirrhosis; CrI, credible interval; DCV, daclatasvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; NC, without cirrhosis; PR, pegylated-interferon alpha and ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TE, Treatment experienced; TN, Treatment naive; 3D/RBV, ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin.

Table 4.16: NMA SVR results (random effects) for GT1b patients (RR (95% CrI))

Comparison EBR/GZR 1-12 vs.	GT1b TN NC patients	GT1b TN C patients	GT1b TE NC patients	GT1b TE C patients
PR 1-48	**1.92 (1.67, 2.25)**	**2.89 (2.11, 4.25)**	**2.58 (2.04, 3.32)**	**3.58 (2.10, 6.13)**
SMV/PR 1-12, PR 13-24 or PR 13-48	**1.24 (1.11, 1.53)**	**1.58 (1.06, 5.45)**	1.22 (0.98, 5.25)	1.27 (0.84, 17.95)
SOF/PR 1-12	1.00 (0.97, 1.09)	1.09 (0.99, 4.37)	1.16 (0.97, 3.37)	1.60 (0.93, 55.93)
LDV/SOF 1-8/12	1.02 (0.97, 1.27)	1.01 (0.96, 1.16)	1.00 (0.89, 1.09)	1.00 (0.70, 1.20)
3D/±RBV 1-12/24	0.99 (0.96, 1.02)	1.01 (0.97, 1.62)	0.99 (0.89, 1.21)	1.02 (0.75, 4.08)
DCV/SOF 1-12	1.00 (0.97, 1.50)	--	1.00 (0.90, 1.79)	--

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00).
Abbreviations. C, with cirrhosis; CrI, credible interval; DCV, daclatasvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; NC, without cirrhosis; PR, pegylated-interferon alpha and ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TE, Treatment experienced; TN, Treatment naive; 3D/RBV, ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin.

Table 4.17: NMA SVR results (random effects) for GT4 patients (RR (95% CrI))

Comparison EBR/GZR 1-12 vs.	GT4 TN NC patients	GT4 TN C patients	GT4 TE NC patients	GT4 TE C patients
PR 1-48	**2.36 (1.57, 3.65)**	**5.26 (2.11, 9.85)**	2.59 (0.91, 3.94)	2.47 (0.06, 5.67)
SMV/PR 1-12, PR 13-24 or PR 13-48	1.09 (0.84, 29.18)	1.23 (0.55, 82.71)	1.43 (0.55, 26.21)	1.45 (0.04, 30.13)
SOF/PR 1-12	--	1.11 (0.50, 2.17)	--	0.96 (0.03, 6.40)
LDV/SOF 1-12	--	1.00 (0.44, 1.21)	1.00 (0.38, 1.14)	0.65 (0.02, 1.09)
2D/RBV 1-12/24	1.00 (0.79, 4.62)	1.02 (0.49, 3.23)	1.00 (0.39, 1.87)	0.68 (0.02, 2.03)
DCV/PR 1-24 or DCV/PR 1-24, PR 25-48	1.35 (0.90, 59.42)	1.25 (0.57, 18.75)	1.34 (0.55, 22.38)	0.70 (0.02, 3.10)
DCV/SOF 1-12	1.00 (0.97, 1.50)	--	1.00 (0.40, 2.11)	--

Note: Values in bold represent those that are statistically meaningful (i.e. the confidence or credible interval does not include 1.00).
Abbreviations. C, with cirrhosis; CrI, credible interval; DCV, daclatasvir; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; NC, without cirrhosis; PR, pegylated-interferon alpha and ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained viral response; TE, Treatment experienced; TN, Treatment naive; 3D/RBV, ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin.

4.4.2 Adverse events results from the NMA

Overall, EBR/GZR had a better safety profile across all outcomes compared to regimens containing pegylated-interferon alpha and/or RBV. Although, data for GT4 were much more limited than for GT1.

ERG comment: As reported above, the ERG has serious concerns with the methodology of both the naïve method and NMA evidence synthesis performed by the company and considers the outcomes of these analyses to be unreliable.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG explored the possibilities to do a proper NMA. However, only four EBR/GZR trials included a relevant comparator. In three of the trials the comparator was placebo. None of the placebo controlled trials reported the number of patients with SVR after 12 weeks; but given the nature of the disease it may be expected that the SVR rate is 0%. Other trials including a placebo control arm (SAPPHIRE-I[21] and II[47]) also did not report the number of patients with SVR. The one remaining trial (C-EDGE H2H) compared EBR/GZR with SOF/PR for 12 weeks. Three other trials included a SOF/PR arm:

- ATOMIC compared SOF/PR for 12 weeks with SOF/PR for 24 weeks. This was the only trial with a SOF/PR-24 arm. Therefore, no further network can be created.
- Pearlman et al. compared SOF/PR for 12 weeks with SMV/SOF for 12 weeks. However, SMV/SOF is not listed as a relevant comparator for EBR/GZR in the NICE scope.
- ELECTRON compared SOF/PR for 12 weeks with SOF/PR for eight weeks, with LDV/SOF for 12 weeks, with LDV/SOF/RBV for 12 weeks, and with SOF/RBV for 12 weeks. However, the SOF/PR arm included only 11 patients with a 100% SVR rate. In addition, the study included patients with GT1, 2 and 3. This means that this study is open to bias and cannot be used for a proper NMA.

Therefore, the ERG concluded that a NMA was not possible given the available data presented in the CS.

4.6 Conclusions of the clinical effectiveness section

The conclusion from the EBR/GZR trials is that EBR/GZR has high SVR rates, especially for patients with GT1a and GT1b. In addition, EBR/GZR has a relative favourable safety and tolerability profile, especially when compared with P and/or RBV containing regimens.

Comparator data (for SVR12 and AEs) were provided by single arms of randomised controlled trials (RCTs), or non-RCTs. Although reported baseline characteristics appear similar between intervention and comparator trials, the possibility that other factors differed across trials cannot be ruled out. The ERG has serious problems with the methodology of both types of evidence synthesis performed by the company and considers the outcomes of these analyses therefore as unreliable.

5 COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Objective of cost effectiveness review

The CS states that a systematic literature review (SLR) was conducted to identify evidence from economic analyses relating to the use of EBR/GZR and relevant comparators for the treatment of chronic hepatitis C (CS, Section 5.1.1). Searches were initially undertaken in October 2015 and updated in January 2016. Searches were reported for MEDLINE, MEDLINE In-Process, Embase, EconLit, Tufts Cost-Effectiveness Analysis Registry, NHS EED and the HTA Database. The database searches were limited from 2005-January 2016. In addition the following resources were searched: NICE, European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), European Congress for Clinical Microbiology and Infectious Diseases (ESCMID), Viral Hepatitis Congress and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European and International Congresses. Conference searches were limited to the most recent two years available.

ERG comment: Most search strategies for the database searches were provided in the Appendix 12 of the CS and are well reported and reproducible. However, the strategies for the Tufts registry and the conference proceeding searches were not provided. These were supplied following a clarification request. The host provider for each database was listed, and the date span of the databases searched and the specific date the searches were conducted were provided. The database searches were clearly structured and used combinations of index terms appropriate to the resource searched, free text and a large number of synonyms for the condition, intervention and comparators. The use of tradenames (such as Zepatier), and additional search terms (such as peginterferon) may have formed useful additions to the search.

Economics and cost filters were included in the NHS EED searches. As this is an economics database the ERG believes it is not necessary to include this facet, as this may result in unnecessarily restricting the results retrieved. Although a validated filter does not appear to have been used or referenced, a wide range of relevant terms was included.

Measurement and value of health effects

The CS states that a systematic literature review (SLR) was conducted to identify relevant HRQoL data for chronic hepatitis C patients (CS, Section 5.4.3) using the databases searched in Section 5.1.1 of the CS. Searches were initially undertaken in October 2015 and updated in January 2016.

ERG comment: Most search strategies for the database searches were provided in the Appendix 15 of the CS, and are well reported and reproducible. The strategies for the Tufts registry and the conference proceeding searches were not documented, however these were provided by the company following a clarification request. The database searches were clearly structured and used combinations of index terms appropriate to the resource searched, free text and a range of synonyms for the condition. The database hosts for each database and the date search conducted were listed, however a specific date span for each database was not included. This additional information was provided following a clarification request. Search terms were used to limit the results to HRQoL studies. Although a validated filter does not appear to have been used or referenced, a wide range of relevant terms was included.

Cost and healthcare resource use identification, measurement and valuation

The CS states that a systematic literature review (SLR) was conducted to identify cost and resource use associated with the treatment of the hepatitis C population (CS, Section 5.5.2). Searches were initially undertaken in October 2015 and updated in January 2016. Searches were reported for MEDLINE, MEDLINE In-Process, Embase, EconLit, Tufts Cost-Effectiveness Analysis Registry, NHS EED and the HTA Database. The database searches were limited from 2005-January 2016.

ERG comment: Most search strategies for the database searches were provided in the Appendix 19 of the CS and are well reported and reproducible. However, the strategies for the Tufts registry and the conference proceeding searches were not provided. These were supplied following a clarification request. The host provider for each database was listed, and the date span of the databases searched and the specific date the searches were conducted were provided. The database searches were clearly structured and used combinations of index terms appropriate to the resource searched, free text and a range of synonyms for the condition. Although a validated filter does not appear to have been used or referenced, a wide range of relevant terms was included.

5.1.2 Inclusion/exclusion criteria used in the study selection

Table 5.1 presents an overview of inclusion and exclusion criteria used for the review.

Table 5.1: Inclusion and exclusion criteria used for the review

Criteria	Include	Exclude
Population	Adults (age ≥18 years) with HCV with or without any co-morbidity (except HIV)	• Healthy volunteers • Children (age <18 years) • HCV+HIV* • Disease other than HCV**
Interventions	Studies assessing the interventions that included at least one of the interventions listed below: • EBR • GZR • BOC • IFN • RBV • DCV • SOF • LDV • All components of 2D/3D • SMV • TVR	• Studies that do not assess at least one of the included interventions are excluded • Studies are excluded on the basis of comparator therapy
Study Type	Full economic evaluations, such as: • Cost–consequence • Cost-minimisation • Cost-effectiveness • Cost–utility • Cost–benefit	• Non-systematic reviews****, letters and comment articles. • Burden of illness studies and non-modelling will be excluded

Criteria	Include	Exclude
Outcomes	• ICER • Costs (unit and total) • QALYs • LYs • Incremental costs • Incremental QALYs/LYs • Model inputs (e.g. transition probabilities, % of patients at fibrosis stage etc.) • Sensitivity analyses results	• No specific exclusion criteria
Language of publication	• Studies published in English • Studies published in non-English languages were included and flagged*****	None
Date of publication	Database searches: 1 January 2005 to 20 January 2016 Conference abstracts: 1 January 2013 to 20 January 2016	None

Source: Based on Table 57 of the CS

Abbreviations. 2D: ombitasvir–paritaprevir–ritonavir; 3D: ombitasvir–paritaprevir–ritonavir with dasabuvir; BOC: boceprevir; DCV: daclatasvir; EBR: elbasvir; GZR: grazoprevir; HCV, hepatitis C virus infection: HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; IFN: interferon; LDV: ledipasvir; Lys: life years; OMV: ombitasvir; PR: pegylated-interferon alpha in combination with ribavirin; PRV: paritaprevir; QALY: quality-adjusted life years; RBV: ribavirin; RTV: ritonavir; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir.

Notes: *, HIV is a devastating disease which severely affects the patients' immune system therefore patients co-infected with HCV and HIV may incur higher costs while their QoL is severely impaired by the co-infection ; **, studies assessing patients with HCV-related liver cancer were included and flagged; ***, studies evaluating BOC+IFN+RBV or TVR+IFN+RBV were included only if these therapies were evaluated against PR either alone or in combination with other protease inhibitors; ****, systematic reviews were included and flagged for bibliography searches; *****, studies published in languages other than English were explored only if sufficient evidence was not identified from English studies.

ERG comment: The reasons provided by the company for their exclusion of the studies with HIV co-infected HCV patients were not clear to the ERG. HIV co-infected patients were mentioned in the final scope[2] and EBR/GZR is expected to be indicated for HIV co-infected HCV patients. By excluding HIV co-infected patients from the cost effectiveness SLR, the company omitted providing sufficient evidence on an important subgroup of the indicated population for EBR/GZR.

It was also not clear why the Scottish Medicine Consortium (SMC) assessment reports for the new treatments in CHC had not been part of the search conducted by the company. After a justification was requested in the clarification letter, in their response,[65] the company mentioned that they do not believe that the limited information presented in the SMC assessment report would allow thorough completion of the data extraction table. The ERG thinks that this reasoning of the company does not justify exclusion of the SMC assessment reports from the search strategy, since some of the SMC assessment reports might have contained more information than the abstracts.

5.1.3 Included/excluded studies in the cost effectiveness review

In the CS, 203 potentially relevant unique studies were identified in the cost effectiveness review. Among these studies identified in the SLR, 32 analyses were conducted in UK. These UK-based studies were considered to be relevant for the decision problem by the company.

No studies have been conducted on the economic analysis of EBR/GZR. A summary table of the published UK cost effectiveness studies was given in Table 58 of the CS, whereas the summary of all identified non-UK studies were presented in the Appendices (Appendix 13) of the CS.[56] Quality assessments of the 32 identified UK cost effectiveness studies were presented in Appendix 14 of the CS. The quality assessments were based on NICE methodology checklist for economic evaluations adapted from Drummond and Jefferson 1996.[66]

As can be seen in Table 58 of the CS, 10 studies focused on the cost effectiveness of different versions of the PR interventions in HCV (e.g. differing in terms of treatment durations, in terms of interferon type, in terms of populations considered or whether response guided therapy administration was followed or not).[67-76] Three of these 10 published studies were HTA documents (Wright et al., 2006,[67] Shepherd et al., 2007[71] and Hartwell et al., 2011[68]). The majority of these studies that analysed the cost effectiveness of PR, (70%) were published before 2011.

In 2011, two NICE technology appraisals were published, namely TA252[77] and TA253[78], for TVR/PR and BOC/PR, respectively. Following these TAs, there were eight other published cost effectiveness studies that compared either TVR/PR and/or BOC/PR with PR [79-86]. These studies focused on different subpopulations (e.g. treatment naïve or treatment experienced) or on different types of therapy (e.g. short duration therapies or response guided therapies of BOC/PR and TVR/PR).

After 2014, 12 cost effectiveness studies were published, which incorporated interventions that included newer DAAs such as SMV, SOF, LDV, DCV and 2D or 3D (i.e. treatment combinations like SMV/PR, SOF/PR, SOF/RBV, LDV/SOF, DCV/SOF with/without RBV, DCV/PR or SMV/SOF).[87] These studies focused on various subpopulations (differing by genotypes, treatment experience status, interferon eligibility, disease severity etc.). Four of these studies were NICE technology appraisals, namely TA 330 (for SOF/PR and SOF/RBV)[88], TA 363 (for LDV/SOF)[89], TA 364 (for DCV/SOF±RBV or DCV/PR)[90] and TA365 (for 2D or 3D)[91].

Most models used in these published studies had similar features. All models were Markov models, most having disease states representing differing stages of disease severity based on METAVIR or fibrosis levels, presence of cirrhosis (compensated and decompensated), presence of hepatocellular carcinoma and liver transplantation, as well as treatment response (sustained virologic response). Most of the studies had a lifetime horizon. The more recent studies had more comparators as well as more subpopulations, reflecting the changing landscape of the HCV treatment.

ERG comment: The ERG detected some reporting errors in the Table 58 of the CS,[1] which summarised study characteristics and outcomes reported in the identified cost effectiveness studies conducted in the UK. For instance, for TA364[90], the costs of DCV/PR for treatment experienced patients with cirrhosis in the DCV/PR comparison; the costs of SMV/PR for treatment naïve patients with cirrhosis were not reported for DCV/SOF comparison; and instead of the costs of SOF/PR, costs of SMV/PR were reported for treatment experienced patients with cirrhosis, just to name a few. These identified errors jeopardise the credibility of the extracted results in Table 58 of the CS.[1]

In addition, the ERG had noticed that both Wright et al., 2006[67] and Grieve et al., 2006[70] were based on the results of the same cost effectiveness analysis. Furthermore, the ERG discovered that the company had omitted to identify TA331,[92] which was the NICE technology appraisal of SMV/PR. In their response to the clarification letter[65], the company confirmed that including both Wright et al., 2006[67] and Grieve et al., 2006[70] as a duplication and the omission of TA331[92] was a mistake. The summary of the characteristics and outcomes of TA331 was additionally provided in the response to the clarification letter.[65]

5.1.4 Conclusions of the cost effectiveness review

No specific conclusions from the economic review were provided in the CS. The ERG thinks that the identified studies 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 5.2 presents a summary of the de novo economic model developed by the company.

Table 5.2: Summary of the company's submitted 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. Same model structure is used for all subpopulations. Treatment for HCV takes place in the first year of the time horizon.	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[68, 71]	Section 5.2.2 (p. 187)
Sub populations	Twelve subpopulation were considered based on categories below: • genotypes: GT1a, GT1b and GT4 • treatment naïve (TN) and treatment experienced (TE). • cirrhotic (C) and non-cirrhotic (NC) This categorisation resulted in the following subpopulations: 1. GT1a, TN, C 2. GT1a, TN, NC 3. GT1a, TE, C 4. GT1a, TE, NC 5. GT1b, TN, C 6. GT1b, TN, NC 7. GT1b, TE, C 8. GT1b, TE, NC 9. GT4, TN, C 10. GT4, TN, NC 11. GT4, TE, C 12. GT4, TE, NC	The subgroups based on genotypes (GT1a, GT1b and GT4); treatment experience (TN and TE) and presence of cirrhosis (C, NC) were considered because of the differences of disease prognosis and effectiveness for chronic HCV treatments between these subgroups.	Section 5.2.1 (p. 187)

	Approach	Source/Justification	Signpost (location in CS)
States and events	The model consists of 13 states. F0-F3 are non-cirrhotic states and F4 was considered as cirrhotic state. • F0: no fibrosis • F1: portal fibrosis without septa • F2: portal fibrosis with septa • F3: portal fibrosis with numerous septa without septa • F4: compensated cirrhosis • SVR F0-F3: F0-F3, achieved SVR after treatment • SVR F4: compensated cirrhosis, achieved SVR after treatment • DC: decompensated cirrhosis • HCC: Hepatocellular carcinoma • LT: First year of liver transplant • PLT: After first year of liver • 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; patients with decompensated cirrhosis (or more severe health state) are not eligible for treatment. 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 achieved SVR are at risk of re-infection. Patients who reached F4 can progress to DC and HCC states, which may lead to liver transplantation and liver related death. Liver transplantation was divided into two categories (1st year of LT and post LT years).	Health states were based upon disease severity. The treatment determines the SVR, adverse event and discontinuation probabilities.	Section 5.2.2 (p. 187)
Comparators	Comparators differ for each of the considered subpopulation. EBR/GZR (EBR and GZR 12w; subpopulations 1-12) BSC (subpopulations: 2, 4, 6, 8, 10 and 12)	They are based on licensed indications and NICE recommendations.	Section 5.2.4 (p. 192)

	Approach	Source/Justification	Signpost (location in CS)
	PR (48w; subpopulations: 1-12) SOF/PR: (SOF 12w; PR 12w; subpopulations: 1-9 and 11) SMV/PR: (12w + PR 24w (subpopulations: 1-12) 3D 12w + RBV 12w (subpopulations 2, 4, 5, and 7) 3D 12w + RBV 24w (subpopulations 1 and 3) 3D 12w (subpopulations 6 and 8) 2D 12w + RBV 12w (subpopulations 10 and 12) 2D 24w + RBV 24w (subpopulations 9 and 11) LDV/SOF 8w (subpopulations 2 and 6) LDV/SOF 12w (subpopulations 1,3-5, 7-9, 11 and 12) DCV 12w + SOF 12w (subpopulations 2, 4, 6, 8 and 12) DCV 24w + PR 24w (subpopulations 9, 10, 11 and 12)		
Natural history	Natural history is based on how disease progresses if a patient does not reach SVR.	The progression rates between F0 and F4 were based on Thein et al. 2008,[93] which is a systematic review and meta-analysis providing state specific progression rates. Transition probabilities after DC are based on Fattovich et al. 1997,[94] which is a natural history study.	Section 5.3.2 (p. 199)
Treatment effectiveness	Treatment influences the probability of reaching SVR, adverse events and discontinuation.	SVR, adverse event and discontinuation probabilities were based on NMA results for EBR/GZR and its comparators. EBR/GZR trials' post-hoc analyses and other input findings from systematic review were used in the NMA comparisons	Section 5.3 (p. 193)
Adverse events	The adverse events considered in the economic model were anaemia, neutropenia, rash, pruritus and nausea.	Five key drug related AEs most commonly observed in EBR/GZR and its comparators are considered.	Section 5.3.1 (p. 195)
Health related QoL	The model uses a state based utilities from the literature (utilities that were used in Wright et al. 2006[67]). Disutilities from adverse events were	Those state-based health utility values were used in previous submissions.	Section 5.4 (p. 201)

	Approach	Source/Justification	Signpost (location in CS)
	applied based on treatment specific utility decrement to baseline utility while on treatment. These decrements were obtained from data on file or independently from previous TAs.[77, 89, 90, 92]		
Resource utilisation and costs	Treatment cost (e.g. technology acquisition and administration costs of EBR/GZR 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.	Section 5.5 (p. 222)
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case	Section 5.2.3 (p.190)
Sensitivity analysis	One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analysis	Ranges based on observed confidence intervals and assumptions.	Section 5.8 (p. 261)

Abbreviations: AE: Adverse event; BOC: boceprevir; 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; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained virological response; TE, treatment experienced; TN, treatment-naïve; TVR, telaprevir; 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 5.3: 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	Yes	Yes, only SMV/SOF, BOC/PR and TVR/PR were not included even though they were included in previous technology appraisals.[89-92]
Type of economic evaluation	Cost-effectiveness analysis	Yes	
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	Time horizon is lifetime, average starting age is 40 for treatment naïve and 45 for treatment experienced population.
Synthesis of evidence in outcomes	Systematic review	Yes	Most parameters were based on the NMA. However, the NMA is not connected for some of the subpopulation and some parameters were identified by a non-systematic search (non-treatment specific probabilities)
Measure of health effects	QALYs	Yes	
Source of data for measurement HRQoL	Reported directly by patients and/or carers.	Yes/No	The HRQoL reported in the EBR/GZR RCTs by patients was not used in the company base case; instead, the patient reported HRQoL from another clinical study were used.
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	

Abbreviations: 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 Population

In the CS, it is mentioned that the patient population included in the economic evaluation reflected the anticipated EMA licenced indication, which is CHC with GT1a, GT1b and GT4.[1] Even though it was mentioned that the anticipated EMA would not distinguish patients by cirrhosis status or treatment history, in the CS, 12 subpopulations were considered based on three categories below:

- genotypes: GT1a, GT1b and GT4
- treatment naïve (TN) and treatment experienced (TE).
- cirrhotic (C) and non-cirrhotic (NC)

This categorisation resulted in the following 12 subpopulations:

1-GT1a, TN, C;	5-GT1b, TN, C;	9-GT4, TN, C;
2-GT1a, TN, NC;	6-GT1b, TN, NC;	10-GT4, TN, NC;
3-GT1a, TE, C;	7-GT1b, TE, C;	11-GT4, TE, C;
4-GT1a, TE, NC;	8-GT1b, TE, NC;	12-GT4, TE, NC.

ERG comment: The population of the cost effectiveness analysis seems to be broadly in line with the scope. In the CS,[1] no evidence was presented on the cost effectiveness of EBR/GZR for some of the subpopulations, namely for the patients whom are co-infected with HIV, patients who have renal impairment, patients who are post-liver transplant, patients who have haemoglobinopathies or patients who are intolerant or ineligible to interferon. Among those populations for which no cost effectiveness evidence was provided, only the non-inclusion for the patients with renal impairments, patients who have haemoglobinopathies and patients that are post-liver transplant were justified due to the lack/paucity of clinical data. The reasons for non-inclusion for other groups (e.g. HIV co-infected) were not very clear to the ERG.

In the CS,[1] the company suggested that patients with HIV co-infection should receive the same treatment duration and regimen as those with HCV mono-infection, referencing EASL 2015 guidelines.[95] The ERG has serious concerns over the generalisability of the current cost effectiveness evidence for HIV co-infected patients. Current evidence is predominantly based on mono-HCV infected patients and for HRQoL, the company even excluded patients co-infected with HIV. Hence, the ERG thinks a separate proper subgroup analysis should have been conducted for HIV co-infected patients.

In a similar manner, the company did not provide any cost effectiveness evidence for patients who are intolerant to or ineligible for interferon treatment. The company rightly stated that EBR/GZR is an interferon free treatment, however this justifies only the fact that EBR/GZR can be a treatment option for this patient group, however this does not bring any additional information over the value for money of EBR/GZR for patients who are intolerant to or ineligible for interferon. The ERG believes that a separate subgroup cost-effectiveness analysis with proper comparators, in which both cost and effectiveness data based on this specific patient subgroup is included, should have been conducted.

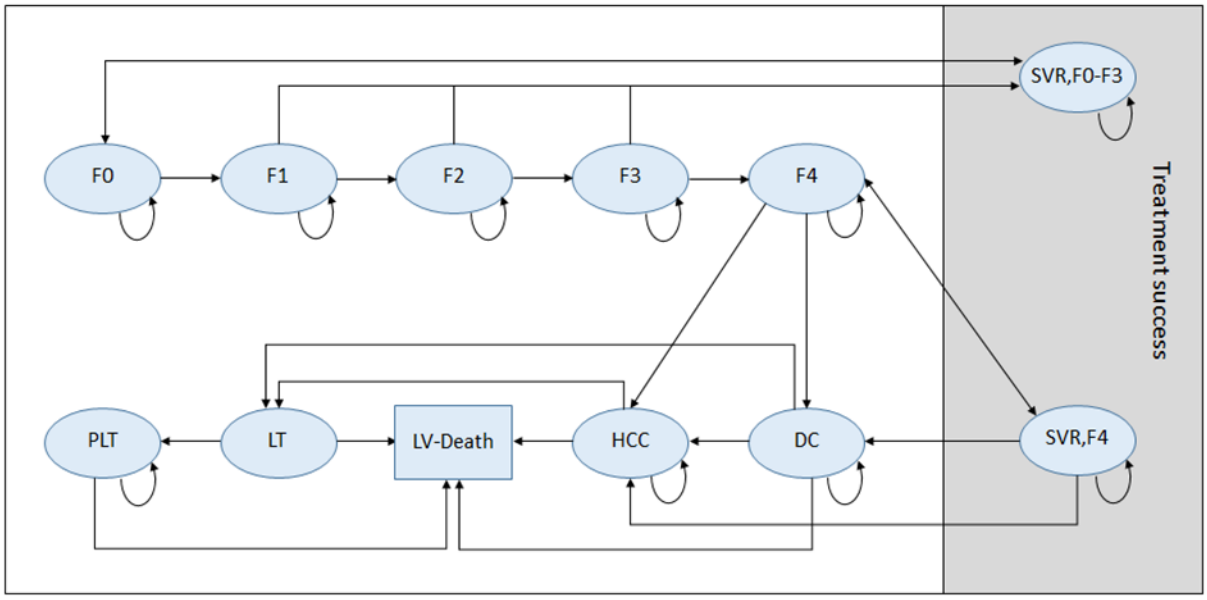
Another issue relates to the heterogeneity of the treatment-experienced population. The previous treatment this group might have received could be a non-DAA treatment like PR, or a DAA, whilst the reason for needing a new treatment could be either intolerance to the previous treatment or an inadequate response. Even though there can be potential clinical differences between these subgroups, in the cost effectiveness analysis these subgroups were assumed to be clinically same and no justification was provided for this assumption.

The ERG thinks that separate analyses for mild (F0-F1) and moderate (F2-F3) non-cirrhotic patients may provide additional insights on the cost effectiveness of EBR/GZR for patients with CHC given potential differences between licensed/recommended comparators, details of the regimens (duration), SVR rates and long term prognosis between patients with mild and moderate disease. In addition, by separating non-cirrhotic patients into two further subpopulations, namely patients with mild (F0-F1) and with moderate (F2-F3) fibrosis, the cost effectiveness of watchful waiting for mild fibrosis patients until they progress (which was listed as a treatment option in the scope of NICE TA 363[89]), would have been possible.

5.2.3 Model structure

The company uses a Markov model to estimate the costs and benefits associated with treatments for hepatitis C. The state transition model consists of 13 health states. The schematic representation of the model is given in Figure 5.1 below (taken from CS Figure 16).

Figure 5.1: Model Structure



* The model consists of the following health states: no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), portal fibrosis with numerous septa without cirrhosis (F3), compensated cirrhosis (F4), decompensated cirrhosis (DC) states, hepatocellular carcinoma (HCC) state, two liver transplant states—first year (LT) and subsequent years: post liver transplant (PLT), liver-related death (LV-Death), death from all other causes (not shown here), and two sustained virologic response (SVR) status states stratified by fibrosis stage – 'SVR, F0–F3' and 'SVR, F4'. As shown by the double arrow lines, re-infection can occur from "SVR,F0-F3" to F0 and from "SVR,F4" to F4. The model assumes that patients cannot get re-infected from "SVR,F0-F3" to F1-F3.

The severity of chronic HCV infection is described by the degree of fibrosis using the METAVIR scoring system. The results of the economic analysis are presented for the non-cirrhotic population (i.e. F0-F3 together) and the cirrhotic population (i.e. F4). The same model structure is used for treatment naïve and treatment experienced patients with GT1a, GT1b and GT4 as well as non-cirrhotic and cirrhotic patients.

Non-cirrhotic patients in the model start in states F0-F3, and cirrhotic patients in the model start in state F4 (compensated cirrhosis). Patients then may either remain in their current health state or move to a more severe health state of liver disease. After reaching compensated cirrhosis, patients are assumed to have a risk of developing decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), which would possibly lead to liver transplantation (LT: first year liver transplant and PLT:

after first year post liver transplant). All these post-cirrhosis states have differing excess risks of liver related death.

During the initial treatment phase of the model, patients receive antiviral drug therapy (first year). All treatment related outcomes are assumed to occur in the first year of the model. It is assumed that patients could not clear from their infection spontaneously and patients do not progress or die in during the treatment period. In the model, after a successful treatment, it is assumed that patients achieve SVR, and patients who do not achieve SVR are at the same risk of disease progression as untreated patients. Non-liver related death can occur in each state.

Non-cirrhotic patients who achieve SVR remain in the current health state unless re-infected. Cirrhotic patients who achieve SVR either can remain in the current health state or can progress onto more severe health states, and they are assumed to have an excess risk of DC and HCC. Patients who received liver transplant assumed to be at no risk of reactivation of HCV.

ERG comment: The model structure is conceptually similar to the models that were recently submitted in previous submissions.[89-91] The ERG thinks that even though the model structure reflects the key elements of the hepatitis C disease progression with and without treatment, there could be more suitable modelling types than a static Markov model. Dynamic modelling approaches could have incorporated the health effects in between individuals within a population by reflecting the effect of HCV treatment in preventing future transmissions. Hence, on a patient population level, the health benefits of more effective treatments with higher SVR rates may have been underestimated, however the magnitude of the underestimation can only be quantified by constructing a de-novo dynamic model.

The current model structure in the CS also only allows the comparison of a single course of treatment used immediately. 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. These aspects of the clinical practice were omitted in the model structure provided in the CS.[1]

In the health economic model, it was assumed that after patients reach SVR, a re-infection would mean that they re-start the course of the disease from F0, which is the health state with no fibrosis. This assumption implies that the liver damage caused by chronic hepatitis C is fully reversible once SVR is achieved. In the CS,[1] no evidence was provided to support this assumption. Furthermore, there is no clinical consensus on the full reversibility of fibrosis caused by hepatitis C, and this approach is against the previous modelling assumptions used in previous NICE TAs (e.g. TA 365[91]). Finally, the ERG's clinical experts suggested that this assumption of fully reversal of fibrosis after SVR might not be always plausible (Personal communication Dr Ryder, 7 June 2016). Therefore, in the additional analyses conducted by ERG, it is assumed that after SVR re-infection, the re-infected patient begins the disease course from his/her pre-SVR health state, and not always from "no fibrosis" state.

5.2.4 Interventions and comparators

Section 3.2 of this report describes the intervention under investigation, i.e. grazoprevir/elbasvir, which is a fixed dose combination of two direct acting antivirals, 50 mg elbasvir and 100 mg grazoprevir. In principle treatment duration is 12 weeks. However, 16 weeks plus ribavirin may be considered in patients with baseline viral load >800,000 IU/ml and/or the presence of specific NS5A RAVs causing at least a five-fold reduction in activity of elbasvir to minimise the risk of treatment failure

In the CS, it was stated that the relevant comparator regimens for EBR/GZR had been selected based on licensed indications and NICE recommendations, and are in line with the final scope.[2] Table 5.4 below gives an overview of the comparators considered in the economic evaluations conducted for each of the patient subpopulations. It was mentioned in the CS that all the treatment durations of the intervention and comparators are based on EMA licences and no response-guided therapy was considered. EBR/GZR treatment duration is in line with the anticipated license. Comparators' treatment durations are informed from NICE TA recommendations and are summarised in Table 5.4, as well.

Table 5.4: Main comparators included in the model

		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
Regimen	**Treatment duration (weeks)**	**C**	**NC**	**C**	**NC**	**C**	**NC**	**C**	**NC**	**C**	**NC**	**C**	**NC**
EBR/GZR	12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BSC	0		✓		✓		✓		✓		✓		✓
PR	48	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SOF/PR	12	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	
SMV/PR	SMV:12w/PR:24w	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2D/3D±RBV	3D:12w/RBV:12w		✓		✓	✓		✓					
	3D:24w/RBV:24w	✓		✓									
	3D:12w						✓		✓				
	2D:12w/RBV:12w										✓		✓
	2D:24w/RBV:24w									✓		✓	
LDV/SOF	8		✓				✓						
	12	✓		✓	✓	✓		✓	✓	✓		✓	✓
DCV/SOF	12		✓		✓		✓		✓				✓
DCV/PR	24									✓	✓	✓	✓

Abbreviations: 2D: ombitasvir/paritaprevir/ritonavir; 3D: ombitasvir/paritaprevir/ritonavir+ dasabuvir; BSC; best supportive care; C: cirrhotic; DCV: daclatasvir-based regimen; EBR: elbasvir; GT: genotype; GZR: grazoprevir; LDV: ledipasvir; NC: non-cirrhotic; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TE: treatment experienced; TN: treatment naïve

ERG comment: The cost effectiveness analysis submitted by the company only considers treatment with EBR/GZR for 12 weeks, thus disregarding the group of GT1a patients with the presence of specific NS5A RAVs causing at least a five-fold reduction in activity of elbasvir who need longer treatment and the addition of ribavirin. In essence, the model simply treats these patients also with 12 weeks of EBR/GZR. In Section 5.3 of this report the ERG will explore how this may impact the outcomes of the cost effectiveness analyses.

The ERG thinks the comparators included in the cost effectiveness analysis were broadly consistent with the final scope. Advice from our clinical expert (Personal communication Dr Ryder, 7 June 2016) confirmed that the included comparators in the CS generally reflect the possible treatment options in the UK clinical practice, only with slight reservations about DCV/SOF for GT1 patients, on the basis of its costs.

In the final scope,[2] boceprevir and telaprevir were included as comparators of EBR/GZR, however these comparators have not been included in the company submission, on the basis that they were no longer considered as current clinical practice. The ERG's clinical expert agreed that indeed these two drugs were no longer used in clinical practice. Furthermore, upon the ERG's request, the company provided the latest available sales data (from IMS England), which demonstrated that total sales of these two agents were negligible (about 1% of total DAA units sold).[65]

Besides boceprevir and telaprevir, the ERG noticed that SMV/SOF could be also a treatment option for HCV patients, especially for interferon ineligible patients.[96] However, NICE could not issue a recommendation for this drug, since the company (which has the selling rights of SMV/SOF) chose not to make an evidence submission for the technology.

Finally, in the CS, both pegylated interferon 2a and pegylated interferon 2b were categorized under one "pegylated interferon" category. The ERG consulted with a clinical expert if this was appropriate, and the ERG was advised that no difference in effectiveness was to be expected between the two versions of pegylated interferon.

5.2.5 Perspective, time horizon and discounting

In the base-case analysis, a lifetime (up to age 100) horizon was chosen and discount rate of 3.5% was used for costs and effects. The model adopted the perspective of NHS/PSS and had a cycle length of one year. Half cycle correction was included in the base case analysis.

ERG comment: The ERG has no specific comments on these choices of perspective, time horizon and the discount rates.

5.2.6 Clinical inputs, treatment effectiveness and extrapolation

In the CS,[1] effectiveness of each HCV treatment was translated to the model in terms of SVR rates. Other treatment specific model input parameters were treatment duration, the discontinuation rate, and treatment related adverse event rates. All other clinical inputs were not related to the treatment (e.g. population characteristics and disease progression probabilities).

As was shown in Section 4.10 of the CS,[1] NMAs were performed in order to identify the appropriate SVR, discontinuation and AE rates for EBR/GZR and its comparators. In the company's base-case, the NMA results from the random effects model were implemented, whereas in a scenario analysis the naïve indirect comparison results were applied. These naïve indirect comparison results were provided

in Appendix 10 of the CS.[56] In the CS, it was stated that the NMA had revealed no significant differences between EBR/GZR and the other all-DAA regimens (LDV/SOF, 2D or 3D, and DCV/SOF) in any of the investigated subgroups. The summary and critique for NMA and naïve indirect treatment approach are discussed in Sections 4.3 and 4.4 of the ERG report.

5.2.6.1 Population characteristics

In the CS model,[1] baseline characteristics from Hartwell et al., 2011[68] were used for the relevant UK population characteristics for treatment naïve and treatment experienced patients with CHC, the distribution of METAVIR fibrosis stages at baseline and proportion of male/female patients. The model was run separately for patients in stages F0-F3 (the non-cirrhotic patients), and stage F4 (cirrhotic patients).

For the age and gender specific all-cause mortality rates, the Office for National Statistics (ONS) interim life tables in England were used.[97] Patient characteristics of the model are summarised in Table 5.5 below.

Table 5.5: Patient characteristics

Characteristic	Base case	Source
Mean age	TN: 40, TE: 45	Hartwell et al., 2011[68]
% Male	70%	
Average weight	79kg	
Distribution of METAVIR fibrosis stage at baseline		
% F0 (in no-cirrhotic population)	TN: 26.0%, TE: 24.0%	Hartwell et al., 2011[68]
% F1 (in no-cirrhotic population)	TN: 26.0%, TE: 24.0%	
% F2 (in no-cirrhotic population)	TN: 24.0%, TE: 26.0%	
% F3 (in no-cirrhotic population)	TN: 24.0%, TE: 26.0%	
% F4 (in cirrhotic population)	TN: 100%, TE: 100%	

Abbreviations: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis; TE, treatment experienced; TN, treatment naïve

ERG comment: The ERG considers the baseline characteristics used in the model to be broadly consistent with the baseline characteristics used in previous cost effectiveness analyses conducted for NICE (e.g. in NICE TA 200[98] and TA 364[90]). The Hartwell et al., 2011[68] study, on which the baseline characteristics of the CS model[1] were based, derived the corresponding data from a range of studies reporting relevant characteristics for UK populations with chronic HCV infection.[99, 100] Note that some of these studies are dating back to the late 1990s, and therefore the ERG has concerns over the validity of using these baseline characteristics that were published more than 15 years ago.

5.2.6.2 SVR Rates

From the 40 trials included in the NMA, eight of them had EBR/GZR as their primary intervention. The trials included in each subpopulation analysis by treatment group and drug are listed in Table 4.12 and Table 4.13 in Section 4.3 of the ERG report.

In the NMA, pooled SVR rates for EBR/GZR were calculated from the corresponding trials and the relative risks obtained from the NMA were applied to the EBR/GZR pooled SVR rates to derive the SVR rates for each relevant comparator in each subpopulation. In the naïve indirect treatment comparison, SVR rates of all comparators were derived from the pooled SVR estimates from the corresponding trials of each comparator.

The SVR rates used in the base-case analysis (from the NMA), and those used in the scenario analysis (from the naïve indirect treatment comparison used in scenario no. 2 in the CS) for GT1a and GT1b subpopulations are given in Table 5.6 and Table 5.7. As it can be seen from these tables, SVR rates for EBR/GZR are the same for both of these approaches.

For the GT4 subpopulation, in the base-case analysis, for EBR/GZR, GT1a absolute SVR rates were applied, whereas for the comparators, the minimum of the GT1a and GT1b relative risks were implemented. Note that in the analysis of CS, relative risk for each comparator was calculated by dividing the SVR rate of EBR/GZR by that of the corresponding comparator; hence, the approach followed by the CS in the base-case chooses the most conservative RR for EBR/GZR from GT1a and GT1b groups. In one of the scenario analysis (i.e. scenario no. 1) in the CS, GT4 specific clinical inputs are applied, which were provided in Appendix 10 of the CS.[56] These GT4 specific SVR rates derived from NMA and indirect naïve treatment comparison are tabulated in Table 5.8.

ERG comment: Not all of the selected studies for the NMA and naïve indirect treatment comparison are based on randomised controlled trials; some of them are either single arm studies or not having relevant comparators. As a result, the original evidence networks for NMAs conducted for SVR were not connected; therefore, some control arms were imputed.

In the alternative method (the naïve indirect treatment comparison), pooled SVR rates of interventions from different studies were compared as if they were from the same trials, without any adjustments. The evidence from this approach is equivalent to that from observational studies and is susceptible to bias.

The concerns of the ERG about the imputation methodology for NMA approach and on the naïve indirect comparison approach were already mentioned in Section 4.4 of this report. In addition to the robustness and susceptibility to bias of these two evidence synthesis approaches, the ERG has also doubts on the accuracy of the pooled SVR estimates that were provided in the CS.[1] These pooled SVR estimates calculated for EBR/GZR were used both in the NMA and in indirect naïve comparison approaches, whereas the pooled estimates for the other comparators are only used in the naïve indirect treatment comparison approach. The ERG could not replicate the reported pooled SVR results of EBR/GZR and its comparators in Appendix 10 of the CS, even though the described steps in Appendix 8 were taken and the data inputs in Appendix 9 were used.[56]

In addition to the indirect treatment comparison related issues, in the CS,[1] it was seen that the statistical analysis approaches for endpoint SVR rates were differing among the EBR/GZR trials. For instance, some studies based their primary endpoint SVR rate calculations on the full analysis set,

some on the modified full analysis set, and some on per protocol population set. Similarly, missing data handling techniques varied as well, where some trials considered missing values and treatment discontinuations as treatment failures, others considered only observed failures. It is unclear to the ERG whether the approaches followed during the derivation of primary endpoint SVR rates and during the derivation of the SVR rates used in indirect treatment comparisons given in Appendix 9 of the CS [56] were the same. Due to these uncertainties and potential inconsistencies, surrounding pooled EBR/GZR SVR rates as well as the concerns on the plausibility and bias susceptibility of the indirect treatment methodologies (NMA and indirect treatment comparison), the ERG suggests that appropriate caution should be applied in the interpretation of the company's analysis results.

Finally, in the CS, for the base-case analysis, SVR rates derived from GT4 group patients were not used due to the limited number of patients, but instead, the minimum of the SVR rate RRs from GT1a and GT1b groups were used as a proxy. The only exception was for 2D/3D, in the CS,[1] it was mentioned that GT1b data was used as a proxy for GT4, by referencing the approach in TA363.[89] However, contrary to the text in the CS, the ERG noticed that in the electronic health economic model, the SVR rates for GT4 patients receiving 2D/3D were derived just like other comparators.

5.2.6.3 Treatment discontinuation

Treatment discontinuation rates related to AEs were modelled using the data from discontinuation occurrences caused by AEs, reported in the clinical trials for EBR/GZR and comparators. The GT1/GT4 trials of included interventions for the NMA of safety outcomes were given in Table 4.14. In the model, it was assumed that discontinuation occurs halfway through the treatment period (e.g. for the EBR/GZR regimen, patients who discontinue are assumed to stop the treatment at week six, half of the treatment duration of 12 weeks). The drug costs and HRQoL for discontinuing patients were adjusted accordingly.

In the CS, the same rate was implemented in both subgroup GT1a and GT1b for EBR/GZR AE discontinuation rates, since they were not available for separate subgroups. For the comparators, relative risks were implemented (relative risk for each comparator is calculated by dividing the discontinuation rate of EBR/GZR by that of the corresponding comparator). Only for 2D/3D treatments, relative risks were estimated separately for GT1a and GT1b subpopulations. For the GT4 subpopulation, the maximum of the GT1a relative risk and GT1b relative risk was taken, which provides the least conservative estimate for 2D/3D. For all other comparators, the same discontinuation rates were implemented for GT1a, GT1b and GT4 subgroups.

The discontinuation rates used in the base-case analysis (from the NMA), and those used in the scenario analysis no 2 in the CS[1] (which were derived from the naïve indirect treatment comparison) are given in Table 5.9 and Table 5.10. Also, GT4 specific discontinuation rates derived from NMA (used in scenario analysis no 1 in CS[1]) and from indirect naïve treatment comparison were tabulated in Table 5.11.

ERG comment: The AE discontinuation results in the CS have the same weakness as the SVR results, since the same evidence synthesis methods were applied in the derivation of both (NMA and the indirect treatment comparison). Therefore, similar to the SVR results, appropriate caution should be applied in the interpretation of the company's analysis results.

In addition, discontinuations may occur for other reasons than adverse events like lack of efficacy or non-adherence to study drug, therefore the ERG considers restricting discontinuation in the model to only being related to adverse events as a limitation.

5.2.6.4 Adverse event rates

The company's model only includes the five key drug-related AEs: anaemia, neutropenia, rash, pruritus and nausea. The EBR/GZR clinical trials did not report these AEs according to severity (i.e. grade 3/4). Therefore, all AEs (not only grade 3/4) were modelled. AE rates based on the whole GT1 population was applied to the GT1a, GT1b and GT4 subpopulations. Only for 2D/3D treatments were AE relative risks estimated separately for GT1a and GT1b subpopulations. For the GT4 subpopulation the maximum of the GT1a relative risk and GT1b relative risk was taken, which provides the least conservative estimate for 2D/3D.

The AE rates used in the base case analysis (from the NMA), and those used in the scenario analysis (from naïve indirect treatment comparison) are given in Table 5.12 and Table 5.13. In addition, GT4 specific AE rates derived from NMA and indirect naïve treatment comparison were tabulated in Table 5.14 and Table 5.15.

ERG comment: AE results in the CS suffer from the same weaknesses as the discontinuation and SVR rate results. Therefore, appropriate caution should be applied in the interpretation of the company's analyses results.

In addition, the reasons behind the choice of these five AEs (anaemia, nausea, neutropenia, pruritus and rash) were not clear for the CS. The ERG believes a transparent inclusion rule for adverse events should have been reported.

Table 5.6: SVR rates for EBR/GZR and relative risk of EBR/GZR versus comparators based on the NMA – base-case

Regimen	Treatment duration (weeks)	Subgroups SVR % for EBR/GZR and relative risk of EBR/GZR versus comparators											
		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	96.2%	96.7%	91.1%	92.7%	100.0%	98.3%	100.0%	99.1%	96.2%	96.7%	91.1%	92.7%
BSC	0	SVR rates assumed to be 0%											
PR	48	2.68	1.86	4.03	2.28	2.89	1.92	3.58	2.58	2.68	1.86	3.58	2.28
SOF/PR	12/12	1.18	1.05	1.33	1.12	1.09	1.00	1.60	1.16	1.09		1.33	
SMV/PR	12/24	1.50	1.20	1.30	1.13	1.58	1.24	1.27	1.22	1.50	1.20	1.27	1.13
2D/3D	3D12/RBV12		0.98		0.96	1.01		1.02					
	3D24/RBV24	1.04		1.00									
	3D12						0.99		0.99				
	2D12/RBV12										0.98		0.96
	2D24/RBV24									1.01		1.00	
LDV/SOF	8		1.01				1.02						
	12	1.00		0.99	0.96	1.01		1.00	1.00	1.00		0.99	0.96
DCV	DCV12/SOF12		0.98		0.97		1.00		1.00				0.97
	DCV24/PR24									0.98	0.98	0.97	0.97

Abbreviations: 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; CIs: confidence intervals; DCV: daclatasvir-based regimen; EBR: elbasvir; GT: genotype; GZR: grazoprevir; LDV: ledipasvir; NC: non-cirrhotic; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained-virologic response; TE: treatment experienced; TN: treatment naïve

Table 5.7: SVR rates for EBR/GZR and relative risk of EBR/GZR versus comparators based on the indirect naïve comparison

Regimen	Treatment duration (weeks)	Subgroups SVR % for EBR/GZR and relative risk of EBR/GZR versus comparators											
		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	96.2%	96.7%	91.1%	92.7%	100.0%	98.3%	100.0%	99.1%	96.2%	96.7%	91.1%	92.7%
BSC	0	SVR rates assumed to be 0%											
PR	48	2.77	1.9	3.46	2.42	2.86	1.95	3.53	2.54	2.77	1.9	3.46	2.42
SOF/PR	12/12	1.19	1.01	1.28	1.15	1.09	1.00	1.92	1.16	1.09		1.28	
SMV/PR	12/24	1.58	1.16	1.23	1.15	1.65	1.19	1.34	1.21	1.58	1.16	1.23	1.15
2D/3D	3D12/RBV12		0.99		0.95	1.00		1.02					
	3D24/RBV24	1.03		0.96									
	3D12						0.98		0.97				
	2D12/RBV12										0.98		0.95
	2D24/RBV24									1.00		0.96	
LDV/SOF	8		1.02				0.99						
	12	0.99		0.99	0.96	1.03		1.08	1.01	0.99		0.99	0.96
DCV	DCV12/SOF12		0.98		0.92		0.97		0.97				0.92
	DCV24/PR24									0.97	0.97	0.92	0.92

Abbreviations: 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; CIs: confidence intervals; DCV: daclatasvir-based regimen; EBR: elbasvir; GT: genotype; GZR: grazoprevir; LDV: ledipasvir; NC: non-cirrhotic; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained-virologic response; TE: treatment experienced; TN: treatment naïve

Table 5.8: SVR rates derived from GT4 specific data (NMA and indirect naïve comparison)

Regimen	Treatment duration (weeks)	SVR % for EBR/GZR and relative risk of EBR/GZR versus comparators							
		GT4 (results from NMA)				GT4 (results from indirect naïve comparison)			
		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	100.0%	97.0%	66.7%	100.0%	100.0 %	97.0%	66.7%	100.0 %
BSC	0	SVR rates assumed to be 0%							
PR	48	5.26	2.36	2.47	2.59	3.14	2.35	2.53	2.59
SOF/PR	12/12	1.11		0.96		1.21		1.05	
SMV/PR	12/24	1.23	1.09	1.45	1.43	1.43	1.10	1.44	1.55
2D/3D	3D12/RBV12								
	3D24/RBV24								
	3D12								
	2D12/RBV12		1.00		1.00		0.93		1.00
	2D24/RBV24	1.02		0.68		1.02		0.69	
LDV/SOF	8								
	12	1.00		0.65	1.00	1.03		0.72	1.04
DCV	DCV12/SOF12				1.00				1.00
	DCV24/PR24	1.25	1.35	0.70	1.34	1.26	1.30	0.86	1.40

Table 5.9: Discontinuation rates for EBR/GZR and relative risks of EBR/GZR versus comparators based on the NMA – base-case

Regimen	Treatment duration (weeks)	Subgroups SVR % for EBR/GZR and relative risk of EBR/GZR versus comparators											
		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%
BSC	0	Not applicable											
PR	48	0.02	0.06	0.02	0.06	0.02	0.06	0.02	0.06	0.02	0.06	0.02	0.06
SOF/PR	12/12	0.01	0.15	0.01	0.15	0.01	0.15	0.01	0.15	0.01		0.01	
SMV/PR	12/24	0.03	0.06	0.03	0.06	0.03	0.06	0.03	0.06	0.03	0.06	0.03	0.06
2D/3D	3D12/RBV12		0.34		0.34	0.03		0.00					
	3D24/RBV24	0.02		0.02									
	3D12						2.86		2.86				
	2D12/RBV12										2.86		2.86
	2D24/RBV24									0.03		0.02	
LDV/SOF	8		3.35				3.35						
	12	0.43		0.43	0.91	0.43		0.43	0.91	0.43		0.43	0.91
DCV	DCV12/SOF12		1.14		1.14		1.14		1.14				1.14
	DCV24/PR24									1.14	1.14	1.14	1.14

Abbreviations: 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; CIs: confidence intervals; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 5.10: Discontinuation rates for EBR/GZR and relative risks of EBR/GZR versus comparators based on the indirect naïve comparison

Regimen	Treatment duration (weeks)	Subgroups Discontinuation % for EBR/GZR and relative risks of EBR/GZR versus comparators											
		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%	0.42%	0.30%
BSC	0	Not applicable											
PR	48	0.17	0.09	0.17	0.09	0.17	0.09	0.17	0.09	0.17	0.09	0.17	0.09
SOF/PR	12/12	0.06	0.26	0.06	0.26	0.06	0.26	0.06	0.26	0.06		0.06	
SMV/PR	12/24	0.22	0.09	0.22	0.09	0.22	0.09	0.22	0.09	0.22	0.09	0.22	0.09
2D/3D	3D12/RBV12		0.56		0.56	0.22		0.22					
	3D24/RBV24	0.18		0.18									
	3D12						5.8		5.8				
	2D12/RBV12										5.8		5.8
	2D24/RBV24									0.22		0.22	
LDV/SOF	8		6.06		6.06		6.06		6.06				0.72
	12	1.56		1.56		1.56		1.56		1.56		1.56	
DCV	DCV12/SOF12		5.18		5.18		5.18		5.18				5.18
	DCV24/PR24									5.18	5.18	5.18	5.18

Abbreviations: 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; C: cirrhotic; CIs: confidence intervals; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 5.11: Discontinuation rates derived from GT4 specific data (NMA and indirect naïve comparison)

Regimen	Treatment duration (weeks)	Discontinuation % for EBR/GZR and relative risks of EBR/GZR versus comparators							
		GT4 (results from NMA)				GT4 (results from indirect naïve comparison)			
		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	5.98%	0.52%	5.98%	0.52%	5.98%	0.52%	5.98%	0.52%
BSC	0	SVR rates assumed to be 0%							
PR	48	0.05	0.02	0.05	0.02	1.17	0.24	1.17	0.24
SOF/PR	12/12	0.09		0.09		1.22		1.22	
SMV/PR	12/24	1.77	0.81	1.77	0.81	10.92	3.81	10.92	3.81
2D/3D	3D12/RBV12								
	3D24/RBV24								
	3D12								
	2D12/RBV12		0.67		0.67		3.54		3.54
	2D24/RBV24	0.13		0.13		2.75		2.75	
LDV/SOF	8								
	12	2.99		2.99	0.64	30.63		30.63	2.70
DCV	DCV12/SOF12				0.38				2.69
	DCV24/PR24	0.08	0.03	0.08	0.03	1.71	0.35	1.71	0.35

Table 5.12: Adverse event rates for EBR/GZR and relative risks of EBR/GZR versus comparators based on the NMA (used in the base-case)

Treatment	Anaemia	Nausea	Rash	Pruritus	Neutropenia
GT1 C					
EBR/GZR	0.4%	3.0%	3.0%	1.5%	0.4%
BSC	N/A	N/A	N/A	N/A	N/A
PR	0.01	0.25	0.09	0.08	0.01
SOF/PR	0.01	0.17	0.18	0.17	0.04
SMV/PR	0.01	0.21	0.08	0.07	0.01
3D/2D	0.02	0.26	0.16	0.32	0.01
LDV/SOF	0.39	0.85	0.47	0.58	0.00
DCV	N/A	N/A	N/A	N/A	N/A
GT1 NC					
EBR/GZR	0.1%	10.3%	2.2%	2.1%	0.2%
BSC	0	0	0	0	0
PR	0.02	0.40	0.10	0.05	0.01
SOF/PR	0.03	0.63	0.28	0.24	0.01
SMV/PR	0.02	0.41	0.12	0.06	0.01
3D/2D	0.06	0.59	0.31	0.17	0.64
LDV/SOF	0.81	1.65	2.08	3.14	0.00
DCV	0.67	0.50	0.73	2.38	0.03
GT4 C					
EBR/GZR	0.4%	3.0%	3.0%	1.5%	0.4%
BSC	N/A	N/A	N/A	N/A	N/A
PR	0.01	0.25	0.09	0.08	0.01
SOF/PR	0.01	0.17	0.18	0.17	0.04
SMV/PR	0.01	0.21	0.08	0.07	0.01
3D/2D	0.03	0.28	0.21	0.44	0.01
LDV/SOF	0.39	0.85	0.47	0.58	0.00
DCV	0.67	0.50	0.73	2.38	0.03
GT4 NC					
EBR/GZR	0.1%	10.3%	2.2%	2.1%	0.2%
BSC	0	0	0	0	0
PR	0.02	0.40	0.10	0.05	0.01
SOF/PR	N/A	N/A	N/A	N/A	N/A
SMV/PR	0.02	0.41	0.12	0.06	0.01
3D/2D	0.75	0.59	0.75	0.39	0.64
LDV/SOF	0.65	1.11	1.26	0.58	0.00
DCV	0.67	0.50	0.73	2.38	0.03

Abbreviations: AEs: adverse events; 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 5.13: Adverse event rates for EBR/GZR versus comparators based on the naïve comparison

Treatment	Anaemia	Nausea	Rash	Pruritus	Neutropenia
GT1 C					
EBR/GZR	0.4%	3.0%	3.0%	1.5%	0.4%
BSC	N/A	N/A	N/A	N/A	N/A
PR	0.02	0.29	0.15	0.1	0.02
SOF/PR	0.02	0.24	0.34	0.19	0.04
SMV/PR	0.02	0.25	0.14	0.09	0.02
3D/2D	0.04	0.29	0.26	0.37	0.02
LDV/SOF	0.74	0.77	0.77	0.59	0.00
DCV	N/A	N/A	N/A	N/A	N/A
GT1 NC					
EBR/GZR	0.1%	10.3%	2.2%	2.1%	0.2%
BSC	0	0	0	0	0
PR	0.02	0.40	0.10	0.05	0.01
SOF/PR	0.03	0.59	0.25	0.24	0.01
SMV/PR	0.02	0.41	0.11	0.06	0.01
3D/2D	0.06	0.54	0.29	0.17	0.57
LDV/SOF	0.4	1.46	1.69	2.78	0.00
DCV	4.14	0.54	0.48	0.97	0.05
GT4 C					
EBR/GZR	0.4%	3.0%	3.0%	1.5%	0.4%
BSC	N/A	N/A	N/A	N/A	N/A
PR	0.02	0.29	0.15	0.1	0.02
SOF/PR	0.02	0.24	0.34	0.19	0.04
SMV/PR	0.02	0.25	0.14	0.09	0.02
3D/2D	0.06	0.33	0.35	0.53	0.02
LDV/SOF	0.74	0.77	0.77	0.59	0.00
DCV	4.14	0.54	0.48	0.97	0.05
GT4 NC					
EBR/GZR	0.1%	10.3%	2.2%	2.1%	0.2%
BSC	0	0	0	0	0
PR	0.02	0.40	0.10	0.05	0.01
SOF	N/A	N/A	N/A	N/A	N/A
SMV	0.02	0.41	0.11	0.06	0.01
3D/2D	1.00	1.25	0.7	0.39	3.19
LDV/SOF	N/A	N/A	N/A	N/A	N/A
DCV	4.14	0.54	0.48	0.97	0.05

Abbreviations. AEs: adverse events; 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 5.14: GT-4 specific adverse event rates for EBR/GZR and relative risks of EBR/GZR versus comparators based on the NMA

Treatment	Anaemia	Nausea	Rash	Pruritus	Neutropenia
GT4 C					
EBR/GZR	0.0%	8.64%	0.0%	0.0%	0.0%
BSC	N/A	N/A	N/A	N/A	N/A
PR	0.03	0.25	0.09	0.03	0.03
SOF/PR	0.06	0.17	0.18	0.08	0.13
SMV/PR	0.08	0.21	0.08	0.05	0.23
3D/2D	0.03	0.28	0.21	0.06	0.01
LDV/SOF	1.85	0.85	0.47	0.25	0.00
DCV	0.04	0.00	0.00	0.03	0.06
GT4 NC					
EBR/GZR	0.0%	5.44%	0.0%	2.49%	0.0%
BSC	0	0	0	0	0
PR	0.01	0.40	0.10	0.01	0.01
SOF/PR	N/A	N/A	N/A	N/A	N/A
SMV/PR	0.04	0.41	0.12	0.03	0.13
3D/2D	0.75	1.28	0.75	0.08	0.64
LDV/SOF	0.61	1.11	0.26	0.37	0.00
DCV+SOF	0.58	0.50	0.73	0.54	0.03
DCV/PR	0.02	0.05	0.73	0.02	0.03

Abbreviations: AEs: adverse events; 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Table 5.15: GT-4 specific adverse event rates for EBR/GZR and relative risks of EBR/GZR versus comparators based on the indirect naïve comparison

Treatment	Anaemia	Nausea	Rash	Pruritus	Neutropenia
GT4 C					
EBR/GZR	0.0%	8.64%	0.0%	0.0%	0.0%
BSC	N/A	N/A	N/A	0.06	N/A
PR	0.06	0.29	0.15	0.12	0.007
SOF/PR	0.11	0.67	0.14	0.04	0.24
SMV/PR	0.08	0.25	0.06	0.05	0.15
3D/2D	0.06	1.65	0.35	0.04	0.02
LDV/SOF	0.25	2.16	0.04	0.06	0.00
DCV	0.04	0.00	0.00	0.03	0.07
GT4 NC					
EBR/GZR	0.0%	5.44%	0.0%	2.49%	0.0%
BSC	0.00	0.00	0.00	0.00	0.00
PR	0.03	0.39	0.10	0.11	0.04
SOF/PR	N/A	N/A	N/A	N/A	N/A
SMV/PR	0.06	0.41	0.04	0.16	0.11
3D/2D	1.00	0.47	0.70	0.51	3.19
LDV/SOF	0.29	0.00	0.14	1.59	0.00
DCV+SOF	1.00	0.35	0.17	1.39	0.05
DCV/PR	0.03	0.54	0.48	0.11	0.05

Abbreviations: AEs: adverse events; 3D/2D: ombitasvir/paritaprevir/ritonavir ± dasabuvir; BSC; best supportive care; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR: peginterferon+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

5.2.6.5 Non-treatment specific transition probabilities

The non-treatment specific transition probabilities used in the company's base-case scenario were mostly sourced from the literature. Transition probabilities between F0-F4 used in the base-case were based on the study by Thein et al. 2008,[93] a systematic review and meta-analysis providing stage-specific progression rates by fibrosis-level. These transition probabilities do not vary by age, however age-specific disease progression probabilities provided in Grishchenko et al. 2009[72] were implemented in a scenario analysis.

Fattovich et al., 1997,[94] a natural history study of a cohort of 384 cirrhotic patients, provided the probability of developing advanced liver diseases from the cirrhotic health state, i.e. from F4 to DC, from F4 to HCC and from DC to HCC. The same study was also used for the transition probability from DC and HCC to liver-related death.

The probabilities of undergoing a liver transplant in patients with DC or HCC were similar to the Wright et al., 2006 study [67]. In that study, the transition probability from DC to liver transplant was originally based on the Siebert et al., 2003[101] study and it was assumed that the transition probability from HCC to liver transplant would be same as the transition probability from DC to liver transplant.

In the model, cirrhotic patients (F4), who achieved SVR can still progress to the DC and HCC health states. For these progression probabilities from F4 with SVR to HCC, estimates were used from a clinical study by Bruno et al., 2007 that only included patients with cirrhosis.[102] For the transition probabilities from F4 with SVR to DC, estimates from Cardoso et al., 2010 study [103] were used. Liver related death following LT and PLT were sourced from the estimates in the Bennett et al., 1997 study.[104]

The re-infection rate was applied from "SVR,F4" to F4 health state and from "SVR,F0-F3" to F0 health state only. The re-infection rate per year was calculated by multiplying the pooled estimate of re-infection among all study participants, as reported in the meta-analysis by Aspinall et al., 2013[105] and the chronicity percentage following re-infection based on Aitken et al., 2008.[106]

Patients achieving SVR were assumed to have a life expectancy equivalent to the general population. The transition probability to death (from non-hepatitis C related causes) is age-dependant and sourced from ONS.[97]

All the non-treatment specific transition probabilities were presented in Table 5.16 below.

ERG comment: The transition probabilities are generally in line with the previous submissions. In the ERG report of TA364, concerns over some of the input sources of transition probabilities had been raised[107]. These concerns were focused on the generalisability and potential outdatedness of the results from Thein et al., 2008 [93], Fattovich et al., 1997[94] and Bennett et al., 1997[104]. Even though the ERG shares the same concerns over these data inputs with Woods et al., 2015[107], due to lack of alternatives, it was decided to use these inputs from the CS.

Table 5.16: Non-treatment specific transition probabilities used in the base-case

Annual transition probabilities	Base case value	Source
F0 to F1	0.117	Thein et al., 2008[93]
F1 to F2	0.085	
F2 to F3	0.120	
F3 to F4	0.116	
F4 to DC	0.039	Fattovich et al., 1997[94]
F4 to HCC	0.014	
DC to HCC	0.014	
DC to LT	0.022	Siebert et al., 2003[101]
HCC to LT	0.022	Wright et al., 2006[67]
DC to LD	0.129	Fattovich et al., 1997[94]
HCC to LD	0.427	
LT to LD	0.210	Bennett et al., 1997[104]
PLT to LD	0.057	
F4 SVR to DC	0.012	Cardoso et al., 2010[103]
F4 SVR to HCC	0.007	Bruno et al., 2007[102]
F4 SVR to F4	0.014	Aspinall et al., 2013[105]; Aitken et al., 2008[106]
F0-F3 SVR to F0	0.014	

Abbreviations: DC: decompensated cirrhosis; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis; HCC: hepatocellular carcinoma; LD: liver disease; LT: liver transplant (1st year); PLT: post liver transplant (subsequent years); SVR: sustained-virologic response

5.2.7 Health-related quality of life

5.2.7.1 Health-related quality of life data from clinical trials

Health-related quality of life was assessed in a number of clinical trials evaluating the efficacy of EBR/GZR, using generic instruments, including EQ-5D-5L. Utilities were derived from the EQ-5D-5L by means of a crosswalk to the three level version of the EQ-5D. The EQ-5D data from the various clinical trials (C-EDGE TN, C-EDGE TE and C-EDGE H2H) were pooled to estimate the impact of EBR/GZR treatment on quality of life. Because of the small number of GT4 patients, GT1 data was used as a proxy for GT4 patients. Patients co-infected with HIV were excluded from the analysis.

The CS presents utilities for all patients (n=497) and separately for European patients only (n=182).[1] No patients from the UK were included. The pooled analysis demonstrated that quality of life for GT1 patients reaching SVR increased over the 12 week period with a utility increment of 0.02 (from 0.83 to 0.85) and 0.03 (from 0.86 to 0.89) for all patients and European patients, respectively.

5.2.7.2 Health-related quality of life data from literature

The CS performed a literature review, which included a total of 111 publications that reported utility values for HCV patients. Among these were six NICE HTAs.[77, 78, 88-91] The utility values reported in Wright et al., 2006[67] were used in three of the six previous NICE submissions and in various published cost effectiveness models. The Wright et al., 2006 study assessed quality of life in patients with mild chronic HCV using EQ-5D. The study compared pegylated-interferon alpha-2B with no treatment over a total follow-up period of 48 weeks. The average utility values in the EBR/GZR clinical trials were higher than those found in the study by Wright et al., 2006. The average utility increment found in the study by Wright et al., 2006 was 0.05, and was larger than reported in the clinical trials.

5.2.7.3 Health-related quality of life data included in the cost effectiveness model

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[67] (Table 5.17). Utility values for more advanced liver disease (DCC, HCC, LT) and PLT were derived from Ratcliffe et al., 2002.[108] Achieving SVR is associated with a 0.05 increase in utility.

These utility values were used in the company's base-case analyses, to be consistent with (three) previous NICE submissions [89-91] and because these utilities were derived from UK patients. The utility increment related to SVR derived from the clinical trials was used in scenario analysis 4; this trial-based utility increment was smaller than that used in the base case analyses (0.03 versus 0.05).

Table 5.17: Utility values used in the cost effectiveness analyses

Health states	Mean	SE	Reference
SVR, F0	0.82	0.04	Wright et al., 2006[67]
SVR, F1	0.82	0.04	
SVR, F2	0.71	0.05	
SVR, F3	0.71	0.05	
SVR, F4	0.60	0.06	
F0	0.77	0.02	
F1	0.77	0.02	
F2	0.66	0.03	
F3	0.66	0.03	
F4	0.55	0.05	
DC	0.45	0.045	Ratcliffe et al., 2002[108]
HCC	0.45	0.045	
LT	0.45	0.045	
PLT	0.67	0.067	

Abbreviations: DC: decompensated cirrhosis; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplant (1st year); PLT: post liver transplant (subsequent years); SVR: sustained-virologic response

Treatment-specific disutilities were applied to adjust for the impact on HRQoL of adverse events. For comparator treatments, these disutilities were derived from previous NICE submissions [77, 89, 90, 92]. A zero utility decrement was applied to 3D/2D, no treatment, and LDV/SOF. Utility decrements for other treatments ranged from 0.035 to 0.145. Treatment-specific disutilities for EBR/GZR were derived from the clinical trials, calculated as the difference between the baseline utility and the mean utility values at week four and end-of-treatment. The mean overall utility decrement for EBR/GZR was 0.000.

In addition, age-dependent utility decrements were included in the model, by means of a linear decrement for age between the ages of 40 and 75 for TN patients and between the ages of 45 and 75 for TE patients. Age-decrements were calculated using data for the general UK population.[109] TE patients have an annual decrement of 0.0035; TN patients have an annual decrement of 0.0049.

ERG comment: Using utilities derived from the literature[67] is consistent with those used in previous STAs.[89-91] However, the ERG considered this a second-best method, as utilities derived from the EBZ/GZR RCTs are available. Although these RCTs did not include patients from the UK, utilities calculated with a UK-specific value set could still have been used in the base-case analyses. This is particularly important because the utilities from the RCTs are substantially higher than those from the

literature used in the model. The company states in the response to the clarification letter[65] that these deviating utilities might be due to differences in geographic regions and disease backgrounds. According to the clinical expert consulted by the ERG (Personal communication Dr Ryder, 7 June 2016), these differences might also be due to changes in patient perspectives over time – where hepatitis C used to be incurable for many patients, the disease can nowadays be managed well with new DAA therapies. As such, the mental impact for patients might be less than before, and quality of life at the start of treatment might be higher. This remark is particularly relevant as the utility values used in the model originate from EQ-5D questionnaires that were completed back in 2002.[67] The utility values for more advanced liver disease originate from data collected in 1998.[108]

Unfortunately, it was not possible for the ERG to construct a scenario using the EQ-5D utilities reported in the CS (Tables 70 and 71) instead of the published utilities, since these utilities were not available per separate health state (F0-F4). However, the estimate of the utility increment associated with SVR was derived from the European patients in the EBR/GZR trials, and was reported in the CS,[1] henceforth the ERG believes that this estimate is a better reflection of the current UK clinical practice.

The EQ-5D-5L instrument was used to elicit patients' quality of life in the RCTs. The EQ-5D-5L value set for the UK should therefore have been used to compute utilities. However, trial-based utilities were calculated using a three level crosswalk algorithm in the CS.[1] Relevant and significant differences exist between this three level crosswalk and the five level value set. The ERG requested trial-based utilities recalculated using the EQ-5D-5L value set. The company declined to provide these utilities, stating that they anticipated that the absolute difference would not be affected.[65] No evidence for this expectation was provided.

The approach used to estimate treatment-specific utility decrements does not seem suited for disentangling the effect of treatment and disutilities from adverse events. Alternatively, the company could have compared the utility value for those patients that had experienced adverse events to the utility values of those patients that did not experience adverse events. However, as the prevalence of adverse events relative to placebo is quite low, the ERG does not expect that using another approach would have resulted in substantially different outcomes in relation to EBR/GZR specific disutilities.

In the cost effectiveness model, quality of life decreases with age. Conceptually, including age-based utility decrements is correct. However, the ERG is not convinced that the approach used by the company is correct. By subtracting utility decrements from the health state utilities, double counting might occur. Age decrements are applied from the age of 40 (45 for TE patients) onwards. Health state utilities were derived from a subset of a larger population of patients that are aged between 21 and 67.[67] As most of these patients are over the age of 40, the impact of age on HRQoL is (implicitly) already taken into account in their utility values. Several alternative approaches could have been used to correctly include age-based decrements. The company could have based the health state utilities only on patients below the age of 40 (45 for TE patients), and then include age-based utility decrements in a linear fashion from that age onwards. However, this would clearly reduce the sample size. Alternatively, health state utility values can be used until age-based utilities from the general UK population are lower. Once age-based utilities are lower the age-based utilities should be used. In this respect, the implicit assumption would be that HCV patients would always have lower or equal utilities as the general population. Based on the utility values of the health states relative to the utility value of the general UK population, this would not have a large impact on the outcomes. In the ERG base-case scenario, the age-based utility decrements are not included to avoid double counting and to

be consistent with the approach conducted in most of the previous STAs (to the best of the ERG's knowledge, the only NICE TA, in which age based utility decrements had been implemented was TA 364[90]).

The ERG noticed also a reporting error in the CS.[1] In Table 75, the health state utility for the SVR F4 state was reported to be 0.49, however in the health economic model, a health state utility of 0.60 had been used. This reporting error has no implications in results, as it is clear that the model uses the correct value.

5.2.8 Resources and costs

Three types of costs were included in the cost effectiveness analyses: cost of treatment (drug acquisition costs), cost of monitoring and follow-up, and costs of adverse events.

5.2.8.1 Drug acquisition costs

The CS states that the list price of EBR/GZR is £12,166.67 per 28-day pack, with weekly costs of £3,041.67. List prices were used for comparator products, whilst dosages were based on summary product characteristics. Weekly cost of EBR/GZR are considerably higher than pegylated-interferon alpha and RBV and higher than for SMV and DVC. Compared to other all-DAA treatments prices are similar. Table 5.18 presents weekly medication costs.

Table 5.18: Drug acquisition costs per week

Therapy	Drug	Weekly cost	Source
EBR/GZR	Zepatier®	£3,041.67	CS[1]
PEG	Weighted sum of Pegasys® & Viraferon Peg®	£130.79	MIMS March 2016[110]
RBV	Weighted sum of Copegus® & Rebetol®	£16.22	eMit[111]
SOF	Sovaldi®	£2,915.25	MIMS March 2016[110]
SMV	Olysio®	£1,866.50	
3D	Sum of Viekirax® and Exviera®	£2,916.67	
2D	Viekirax®	£2,683.33	
LDV/SOF	Harvoni®	£3,248.33	
DCV	Daklinza®	£2,043.15	

5.2.8.2 Monitoring and health state unit costs and resource use

Monitoring costs as defined in the CS refer to the costs encountered when patients are being treated with EBR/GZR or the comparator treatments. These costs per regimen vary according to the treatment duration. The monitoring costs were derived from a previous NICE appraisal[89] and consisted of outpatient appointments, inpatient care, tests and investigations. These costs were assumed to be the same for the all-DAA treatments. Initial evaluation monitoring costs differed for cirrhotic and non-cirrhotic patients; these initial evaluation/monitoring costs were not incurred by treatment-experienced patients. No differences in monitoring costs were assumed between genotypes, apart from the fact that for some treatments treatment duration differs by genotype, and hence the costs of monitoring during active treatment (see Table 5.19).

Table 5.19: Initial evaluation and further investigation costs for cirrhotic/non-cirrhotic patients and monitoring costs during active treatment

	Initial evaluation	Further investigation		
Non-cirrhotic	£642.72	£480.51		
Cirrhotic	£838.59	£480.51		
	Weeks active treatment			
	8	12	24	48
Non-cirrhotic				
EBR/GZR		£1,144.65		
PR				£2,626.98
SOF/PR		£1,144.65		
SMV/PR			£1,913.87	
2D/3D		£1,144.65	£1,392.56	
LDV/SOF	£1,020.19	£1,144.65		
DCV		£1,144.65	£1,392.56	
Cirrhotic				
EBR/GZR		£1,145.67		
PR				£3,794.08
SOF/PR		£1,145.67		
SMV/PR			£2,421.93	
2D/3D		£1,145.67	£1,394.60	
LDV/SOF	£1,022.23	£1,145.67		
DCV		£1,145.67	£1,394.60	

Abbreviations: 3D: ombitasvir/paritaprevir/ritonavir+dasabuvir; DCV: daclatasvir-based regimen; EBR: elbasvir; GZR: grazoprevir; LDV: ledipasvir; PR, peginterferon plus ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir

Health-state unit costs were derived from previous publications[67, 72, 112] and inflated to 2014/15 values. The same costs were applied to all genotypes and all subgroups, see Table 5.20.

Table 5.20: Health state costs (inflated)

Cost Parameter	Mean	SE	Reference
SVR, F0	£237.01	£27.71	Grishchenko et al., 2009[72]
SVR, F1	£237.01	£27.71	
SVR, F2	£289.81	£33.88	
SVR, F3	£289.81	£33.88	
SVR, F4	£512.75	£59.94	
F0	£189.27	£157.73	Wright et al., 2006[67]
F1	£189.27	£157.73	
F2	£983.40	£104.33	
F3	£983.40	£104.33	
F4	£1,560.82	£307.23	
DC	£12,508.53	£2,083.38	
HCC	£11,146.58	£2,619.42	
LT - liver transplant	£37,484.43	£3,956.63	Longworth et al., 2001[112]
LT - care in year in which transplant occurs	£12,972.11	£3,494.66	
PLT	£1,899.60	£486.93	

Abbreviations: DC: decompensated cirrhosis; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis;

HCC: hepatocellular carcinoma; LD: liver disease; LT: liver transplant (1st year); PLT: post liver transplant (subsequent years); SVR: sustained-virologic response

5.2.8.3 Adverse reaction unit costs and resource use

Different drugs were used to treat treatment-related adverse events, for which costs were included in the model. Dosage and usage of these drugs were based on previous submissions [77, 89] and validated by clinical experts. Drug costs were derived from MIMS[110] and eMit.[111] In addition to drug costs, adverse events resulted in additional costs related to outpatient and specialist visits. The type of care provided to manage the adverse event was based on KOL opinion from a previous submission.[89] The total costs per adverse event can be found in Table 5.21.

Table 5.21: Total adverse event costs

Adverse event	Costs
Anaemia	£487.23
Neutropenia	£1,329.18
Rash	£611.21
Pruritus	£0.84
Nausea	£0.78

ERG comment: Overall the ERG has few comments to make to the company's approach to including costs in the cost effectiveness analysis. However, from the CS it was not clear how complete the estimates of the health-state costs are. For example, it was unclear whether also allied health care, GP visits, or home care had been included. This issue was addressed in the clarification letter, and in their response the company referred to the sources of the health state costs. From these sources,[67, 72, 112] it is clear that neither allied health care nor GP visits nor home care had been included. Whilst it might be reasonable to assume that GP costs and allied health care costs will be relatively small compared to hospital admissions and outpatient visits, this is less clear for home care, especially for patients with hepatocellular carcinoma or decompensated cirrhosis. The ERG looked at the cost and resource utilisation studies identified by the company, but none of them reported home care use.

The company states in their submission that the analyses cannot adequately capture the cost effectiveness of EBR/GZR, because CMU prices were not available and list prices had to be used instead. According to the company, the results should be interpreted as indicative and do not reflect real cost effectiveness estimates.

5.2.9 Base-case analysis

5.2.9.1 Summary of base-case de novo analysis inputs

Summary of the inputs of the model are given in Table 5.22 below.

Table 5.22: Summary of variables applied in the economic model

Parameter	Value Selected	Distribution	a	b	Reference in the ERG report
Cohort characteristics					
Age					
Treatment naïve	40	Not included in PSA			Section 5.2.6.1
Treatment experienced	45				
% Male	0.70				
Distribution of METAVIR fibrosis stages at baseline					
% F0	0.165	Beta tree	83.5	422.56	Section 5.2.6.1
% F1	0.165	Beta tree	83.5	422.56	
% F2	0.175	Beta tree	82.5	388.93	
% F3	0.175	Beta tree	82.5	388.93	
% F4	0.320	Beta tree	68	144.5	
% Reinfection per year	0.024	Beta	97.64	4039.65	
% Chronicity following reinfection	0.591	Beta	40.91	28.32	
Natural history annual transition probabilities					
F0 to F1	0.117	Beta	88.3	666.40	Section 5.2.6.5
F1 to F2	0.085	Beta	91.5	984.97	
F2 to F3	0.120	Beta	88	645.33	
F3 to F4	0.116	Beta	88.4	673.67	
F4 to DC	0.039	Beta	96.11	2373.74	
F4 to HCC	0.014	Beta	98.56	6741.40	
DC to HCC	0.014	Beta	98.56	6741.40	
DC to LT	0.022	Beta	97.8	4347.65	
HCC to LT	0.022	Beta	97.8	4347.65	
DC to Liver-related death	0.129	Beta	87.06	585.45	
HCC to Liver-related death	0.427	Beta	57.28	76.78	
LT to Liver-related death	0.210	Beta	79	297.19	
PLT to Liver-related death	0.057	Beta	94.3	1560.09	
F4 SVR to DC	0.012	Beta	98.76	7865.76	
F4 SVR to HCC	0.007	Beta	2.58	389.78	
F4 SVR to F3 SVR	0.000	Beta	0	0	
F4 SVR to F4	0.014	Not included in PSA			
F0-F3 SVR to F0	0.014				
Treatment characteristics					
SVR rates					
EBR/GZR	0.927	Beta	48.49	3.85	Section 5.2.6.2
No Treatment	0.000	Beta	0	0	
vs PR	2.280	Lognormal	-4.99	2.80	
vs SOF/PR	N/A	Lognormal	N/A	N/A	
vs SMV/PR	1.130	Lognormal	-0.10	0.01	
vs 3D/2D	0.960	Lognormal	0.03	<0.01	
vs LDV/SOF	0.960	Lognormal	0.03	<0.01	
vs DCV/SOF	0.970	Lognormal	0.02	<0.01	
vs DCV/PR	0.970	Lognormal	0.02	<0.01	
Treatment discontinuation rate					
EBR/GZR	0.003	Beta	1.38	458.23	Section 5.2.6.3
No Treatment	0.000	Beta	0	0	
vs PR	0.060	Lognormal	<0.01	0.01	

Parameter	Value Selected	Distribution	a	b	Reference in the ERG report
vs SOF/PR	N/A	Lognormal	N/A	N/A	
vs SMV/PR	0.060	Lognormal	<0.01	<0.01	
vs 3D/2D	2.860	Lognormal	-0.68	0.44	
vs LDV/SOF	0.910	Lognormal	<0.01	<0.01	
vs DCV/SOF	1.140	Lognormal	>-0.01	<0.01	
vs DCV/PR	1.140	Lognormal	>-0.01	<0.01	
Treatment duration in weeks					
EBR/GZR	12	Not included in PSA			Section 5.2.4
No Treatment	0				
vs PR	48				
vs SOF/PR	N/A				
vs SMV/PR	24				
vs 3D/2D	12				
vs LDV/SOF	12				
vs DCV/SOF	12				
vs DCV/PR	24				
Adverse event rates					
Anaemia					
EBR/GZR	0.001	Beta	0.18	205.31	Section 5.2.6.4
No Treatment	0.000	Beta	0	0	
vs PR	0.020	Lognormal	<0.01	<0.01	
vs SOF/PR	N/A	Lognormal	N/A	N/A	
vs SMV/PR	0.020	Lognormal	<0.01	<0.01	
vs 3D/2D	0.750	Lognormal	0.02	<0.01	
vs LDV/SOF	0.650	Lognormal	0.01	<0.01	
vs DCV/SOF	0.670	Lognormal	0.01	<0.01	
vs DCV/PR	0.670	Lognormal	0.01	<0.01	
Nausea					
EBR/GZR	0.103	Beta	91.06	794.74	Section 5.2.6.4
No Treatment	0.000	Beta	0	0	
vs PR	0.400	Lognormal	0.07	0.10	
vs SOF	N/A	Lognormal	N/A	N/A	
vs SMV	0.410	Lognormal	0.05	0.07	
vs 3D/2D	1.280	Lognormal	-0.26	0.06	
vs LDV/SOF	1.110	Lognormal	-0.06	<0.01	
vs DCV/SOF	0.500	Lognormal	0.03	0.03	
vs DCV/PR	0.500	Lognormal	0.03	0.03	
Rash					
EBR/GZR	0.022	Beta	19.62	856.31	Section 5.2.6.4
No Treatment	0.000	Beta	0	0	
vs PR	0.100	Lognormal	<0.01	0.04	
vs SOF	N/A	Lognormal	N/A	N/A	
vs SMV	0.120	Lognormal	<0.01	0.03	
vs 3D/2D	0.750	Lognormal	0.05	0.02	
vs LDV/SOF	1.260	Lognormal	-0.09	0.02	
vs DCV/SOF	0.730	Lognormal	<0.01	<0.01	
vs DCV/PR	0.730	Lognormal	<0.01	<0.01	
Pruritus					

Parameter	Value Selected	Distribution	a	b	Reference in the ERG report
EBR/GZR	0.021	Beta	18.59	871.08	
No Treatment	0.000	Beta	0	0	
vs PR	0.050	Lognormal	<0.01	0.02	
vs SOF	N/A	Lognormal	N/A	N/A	
vs SMV	0.060	Lognormal	<0.01	0.02	
vs 3D/2D	0.390	Lognormal	0.04	0.07	
vs LDV/SOF	1.360	Lognormal	-0.16	0.04	
vs DCV/SOF	2.380	Lognormal	-0.96	0.55	
vs DCV/PR	2.380	Lognormal	-0.96	0.55	
Neutropenia					
EBR/GZR	0.002	Beta	0.57	336.18	Section 5.2.6.4
No Treatment	0.000	Beta	0	0	
vs PR	0.010	Lognormal	<0.01	<0.01	
vs SOF/PR	N/A	Lognormal	N/A	N/A	
vs SMV/PR	0.010	Lognormal	<0.01	<0.01	
vs 3D/2D	0.640	Lognormal	0.01	<0.01	
vs LDV/SOF	0.000	Lognormal	0	0	
vs DCV/SOF	0.030	Lognormal	<0.01	<0.01	
vs DCV/PR	0.030	Lognormal	<0.01	<0.01	
Economic Inputs					
Weekly drug costs					
EBR/GZR	£3,041.67	Gamma	100	30.42	Section 5.2.8.1
No Treatment	£0.00	Gamma	0	0	
PR	£146.24	Gamma	100	1.46	
SOF/PR	N/A	Gamma	N/A	N/A	
SMV/PR	£1,079.49	Gamma	100	10.79	
3D/2D	£2,932.91	Gamma	Based on the 3D/2D regimen of the selected subgroup		
3D+RBV	£2,932.91				
3D	£2,699.58				
2D+RBV	£2,916.67				
LDV/SOF	£3,248.33	Gamma	100	32.48	
DCV/SOF	£4,958.40	Gamma	100	49.58	
DCV/PR	£2,189.40	Gamma	100	21.89	
Monitoring costs					
EBR/GZR	between £1,625.16 and £2,464.77	Gamma	Based on the selected subgroup		Section 5.2.8.2
No Treatment	£0.00	Gamma	0	0	
PR	between £3,107.49 and £5,113.18	Gamma	Based on the selected subgroup		
SOF/PR	between £1,625.16 and £2,464.77	Gamma	Based on the selected subgroup		
SMV/PR	between	Gamma	Based on the		

Parameter	Value Selected	Distribution	a	b	Reference in the ERG report
	£2,394.38 and £3,741.03		selected subgroup		
3D/2D	between £1,625.16 and £2,713.70	Gamma	Based on the selected subgroup		
LDV/SOF	between £1,625.16 and £2,464.77	Gamma	Based on the selected subgroup		
DCV/SOF	between £1,625.16 and £2,267.88	Gamma	Based on the selected subgroup		
DCV/PR	between £1,873.07 and £2,713.70	Gamma	Based on the selected subgroup		
Annual costs for health states					
SVR, F0	£237.01	Gamma	73.19	3.24	Section 5.2.8.2
SVR, F1	£237.01	Gamma	73.19	3.24	
SVR, F2	£289.81	Gamma	73.19	3.96	
SVR, F3	£289.81	Gamma	73.19	3.96	
SVR, F4	£512.75	Gamma	73.19	7.01	
F0	£189.27	Gamma	1.44	131.44	
F1	£189.27	Gamma	1.44	131.44	
F2	£983.40	Gamma	88.85	11.07	
F3	£983.40	Gamma	88.85	11.07	
F4	£1,560.82	Gamma	25.81	60.47	
DC	£12,508.53	Gamma	36.05	347.00	
HCC	£11,146.58	Gamma	18.11	615.56	
LT-transplant	£37,484.43	Gamma	89.75	417.64	
LT-care	£12,972.11	Gamma	13.78	941.45	
PLT	£1,899.60	Gamma	15.22	124.82	
Adverse event cost per episode					
Anaemia	£487.23	Gamma	100	4.87	Section 5.2.8.3
Nausea	£0.78	Gamma	100	0.01	
Neutropenia	£1,329.18	Gamma	100	13.29	
Pruritus	£0.84	Gamma	100	0.01	
Rash	£611.21	Gamma	100	6.11	
One-off average adverse event cost (per treatment)					
EBR/GZR	£16	Not included in PSA			Section 5.2.8.3
No Treatment	£0				
PR	£385				
SOF/PR	N/A				
SMV/PR	£362				
3D/2D	£22				
LDV/SOF	£12				

Parameter	Value Selected	Distribution	a	b	Reference in the ERG report
DCV/SOF DCV/PR	£95 £95				
Discount rates for costs	0.035	Not included in PSA			
Health State Utilities					
On-treatment disutilities					
EBR/GZR No Treatment	0.000 0.000	Beta Beta	0 0	0 0	Section 5.2.7.3
PR	between -0.126 and -0.109	Beta	Based on the selected subgroup		
SOF/PR	-0.145	Beta	N/A	N/A	
SMV/PR	Between -0.119 and -0.081	Beta	Based on the selected subgroup		
3D/2D	0.000	Beta	0	0	
LDV/SOF	0.000	Beta	0	0	
DCV/SOF	-0.035	Beta	96.5	2660.64	
DCV/PR	-0.137	Beta	86.3	543.63	
Utility increment due to SVR	0.050	Beta	95	1805	
Utilities after treatment					
SVR, F0	0.820	Beta	75.65	16.61	Sectio5.2.7.3
SVR, F1	0.820	Beta	75.65	16.61	
SVR, F2	0.710	Beta	58.48	23.88	
SVR, F3	0.710	Beta	58.48	23.88	
SVR, F4	0.600	Beta	40	26.67	
F0	0.770	Beta	340.92	101.83	
F1	0.770	Beta	340.92	101.83	
F2	0.660	Beta	164.56	84.77	
F3	0.660	Beta	164.56	84.77	
F4	0.550	Beta	54.45	44.55	
DC	0.450	Beta	55	67.22	
HCC	0.450	Beta	55	67.22	
LT	0.450	Beta	55	67.22	
PLT	0.670	Beta	33	16.25	
Discount rates for effects	0.035	Not included in PSA			

5.2.9.2 Base-case incremental cost effectiveness results

The base-case pairwise incremental cost effectiveness results for comparisons of EBR/GZR and its relevant comparators versus PR across all the different populations are listed in Table 5.23 for GT1a patients, in Table 5.24 for GT1b patients and in Table 5.25 for GT4. It should be noted that all the analyses in the CS were based on the list prices, hence the results should be considered as indicative. Also note that for GT1a TN NC, GT1a TE NC, GT1b TN C and GT1b TE C populations, 2D/3D corresponds to the treatment course of 3D in combination with ribavirin for 12 weeks. For GT1a TN C and GT1a TE C, 2D/3D refers to the treatment course of 3D in combination with ribavirin for 24 weeks. For GT1b TN NC and GT1b TE NC, a treatment course of 3D for 12 weeks is applied and for

GT4 patients 2D in combination with ribavirin is administered during 12 weeks for patients without cirrhosis, and 24 weeks for patients with cirrhosis. Similar to 2D/3D, length of treatment course for LDV/SOF also differs among different populations. For GT1a TN NC and GT1b TN NC patients, LDF/SOF is administered for 8 weeks and for all other licensed populations, LDV/SOF is applied 12 weeks.

In all subgroups, PR was the treatment that resulted in minimum costs, therefore PR was taken as a reference and pairwise incremental results of all other treatments vs PR were given.

For GT1a and GT4 populations, ICER (compared to PR) values for EBR/GZR were around £9,000 per QALY gained for TN and around £8,000 per QALY gained for TE patients. For GT1b, in the TN populations, ICER (compared to PR) values were around £8,000 per QALY gained, whereas for the TE populations, ICER values were about £6,000 per QALY gained.

Next to the pairwise incremental results with PR, in the Appendix 22 of the CS,[56] full incremental analysis results were also presented. From the full incremental analysis, EBR/GZR appeared to be cost effective only in GT1a TN C, GT1a TE C and GT4 TE C populations. In all other populations, EBR/GZR was either dominated by the other cost effective interventions, or the ICER values compared to the previous cost effective interventions were above the £20,000 per QALY gained threshold.

Table 5.23: Base-case analyses for GT1a (TN/TE; C/NC), all comparisons against PR

GT1a TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,599	7.741	-	-	-
SOF/PR	£64,907	8.845	£10,308	1.104	£9,338
SMV/PR	£65,380	8.456	£10,781	0.714	£15,095
EBR/GZR	£68,555	9.260	£13,956	1.518	£9,193
LDV/SOF	£70,941	9.259	£16,342	1.518	£10,765
2D/3D	£96,765	9.208	£42,166	1.467	£28,742
GT1a TN NC Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£26,580	13.473	-	-	-
BSC	£30,513	11.404	£3,932	-2.069	Dominated
LDV/SOF	£32,059	15.098	£5,479	1.625	£3,371
SMV/PR	£36,693	14.550	£10,113	1.077	£9,388
2D/3D	£40,479	15.225	£13,899	1.752	£7,935
EBR/GZR	£42,389	15.150	£15,809	1.677	£9,427
SOF/PR	£43,855	14.942	£17,275	1.469	£11,762
DCV/SOF	£64,902	15.217	£38,321	1.744	£21,976
GT1a TE C Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£55,175	7.447	-	-	-
SMV/PR	£61,679	8.592	£6,504	1.145	£5,681
SOF/PR	£65,426	8.513	£10,252	1.066	£9,616
EBR/GZR	£67,287	9.116	£12,113	1.669	£7,257
LDV/SOF	£69,467	9.139	£14,292	1.692	£8,448
2D/3D	£94,679	9.160	£39,504	1.713	£23,062
GT1a TE NC Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£27,836	12.806	-	-	-
BSC	£28,835	11.271	£999	-1.535	Dominated
SMV/PR	£34,982	14.203	£7,146	1.398	£5,112
2D/3D	£39,915	14.713	£12,079	1.907	£6,334
EBR/GZR	£42,298	14.578	£14,462	1.773	£8,159
LDV/SOF	£43,747	14.713	£15,911	1.907	£8,343
SOF/PR	£45,111	14.198	£17,275	1.393	£12,403
DCV/SOF	£64,599	14.670	£36,763	1.864	£19,718

Abbreviations:.ICER:incremental cost effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

Table 5.24: Base-case analyses for GT1b (TN/TE; C/NC), all comparisons against PR

GT1b TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,884	7.709	-	-	-
SOF/PR	£62,628	9.107	£7,743	1.398	£5,538
2D/3D	£64,947	9.327	£10,062	1.618	£6,217
SMV/PR	£65,571	8.434	£10,687	0.725	£14,741
EBR/GZR	£67,714	9.356	£12,829	1.647	£7,787
LDV/SOF	£70,320	9.331	£15,436	1.622	£9,517
GT1b TN NC Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£26,800	13.442	-	-	-
BSC	£30,513	11.404	£3,712	-2.039	Dominated
LDV/SOF	£31,899	15.120	£5,099	1.678	£3,039
SMV/PR	£37,062	14.499	£10,262	1.057	£9,710
2D/3D	£40,232	15.246	£13,432	1.804	£7,446
EBR/GZR	£41,963	15.209	£15,162	1.766	£8,585
SOF/PR	£42,161	15.175	£15,361	1.733	£8,865
DCV/SOF	£65,018	15.201	£38,218	1.758	£21,739
GT1b TE C Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£54,008	7.577	-	-	-
SMV/PR	£59,760	8.806	£5,751	1.229	£4,680
2D/3D	£62,754	9.285	£8,746	1.708	£5,122
EBR/GZR	£65,304	9.337	£11,296	1.760	£6,418
SOF/PR	£66,777	8.363	£12,769	0.786	£16,253
LDV/SOF	£67,689	9.337	£13,681	1.760	£7,773
GT1b TE NC Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£28,407	12.730	-	-	-
BSC	£28,835	11.271	£428	-1.459	Dominated
SMV/PR	£35,177	14.178	£6,770	1.448	£4,676
2D/3D	£38,905	14.835	£10,499	2.105	£4,988
EBR/GZR	£40,595	14.804	£12,188	2.074	£5,877
LDV/SOF	£43,060	14.804	£14,654	2.074	£7,066
SOF/PR	£44,393	14.293	£15,987	1.564	£10,225
DCV/SOF	£63,650	14.796	£35,244	2.066	£17,060

Abbreviations:.ICER:incremental cost effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

Table 5.25: Base-case analyses for GT4 (TN/TE; C/NC), all comparisons against PR

GT4 TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,599	7.741	-	-	-
SOF/PR	£63,401	9.018	£8,802	1.277	£6,894
SMV/PR	£65,380	8.456	£10,781	0.714	£15,095
EBR/GZR	£68,555	9.260	£13,956	1.518	£9,193
LDV/SOF	£70,941	9.259	£16,342	1.518	£10,765
DCV/PR	£84,350	9.301	£29,750	1.560	£19,076
2D/3D	£93,333	9.282	£38,734	1.541	£25,138
GT4 TN NC Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£26,580	13.473	-	-	-
BSC	£30,513	11.404	£3,932	-2.069	Dominated
SMV/PR	£36,693	14.550	£10,113	1.077	£9,388
2D/3D	£37,785	15.225	£11,204	1.752	£6,396
EBR/GZR	£42,389	15.150	£15,809	1.677	£9,427
DCV/PR	£58,178	15.207	£31,598	1.735	£18,217
GT4 TE C Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£54,551	7.517	-	-	-
SMV/PR	£61,311	8.633	£6,760	1.116	£6,055
SOF/PR	£65,426	8.513	£10,875	0.997	£10,911
EBR/GZR	£67,287	9.116	£12,736	1.600	£7,962
LDV/SOF	£69,467	9.139	£14,916	1.622	£9,194
DCV/PR	£82,894	9.178	£28,343	1.662	£17,054
2D/3D	£91,857	9.164	£37,306	1.647	£22,645
GT4 TE NC Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£27,836	12.806	-	-	-
BSC	£28,835	11.271	£999	-1.535	Dominated
SMV/PR	£34,982	14.203	£7,146	1.398	£5,112
2D/3D	£37,220	14.713	£9,384	1.907	£4,920
EBR/GZR	£42,298	14.578	£14,462	1.773	£8,159
LDV/SOF	£43,747	14.713	£15,911	1.907	£8,343
DCV/PR	£57,873	14.664	£30,037	1.859	£16,160
DCV/SOF	£64,599	14.670	£36,763	1.864	£19,718

Abbreviations:.ICER:incremental cost-effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

5.2.9.3 Clinical outcomes from the model

EBR/GZR as well as other all-DAA regimes (DC/SOF, 2D/3D, DCV/SOF) were the treatments that resulted in highest QALYs for GT1a and GT1b group hepatitis C patients. For GT4 group patients, DCV/PR was also generating as much QALYs as other all-DAA treatments. The disaggregated QALYs by health states and Markov traces were provided in the Section 5.7 of the CS.[1] From these, it could be observed that patients that were treated with all-DAA regimens spend more time in SVR states and spend less time in disease states (F0-F4 and liver disease related states like HCC, DC, LT and PLT) compared to those treated with PR.

5.2.9.4 Cost outcomes from the model

EBR/GZR and all other all-DAA treatments resulted in higher total costs compared to PR and SMV/PR. The substantial list price differences between the drugs were reflected in their total costs. Overall, it could be observed (CS Tables 109-120[1]) that all-DAA drugs led to higher treatment costs, but less monitoring and health state related costs compared to PR. Since AE costs constitute only a small part of total costs, changes in AE costs did not contribute much to the incremental cost results.

5.2.10 Sensitivity analyses

5.2.10.1 Probabilistic sensitivity analysis

The probabilistic sensitivity analyses (PSA) were conducted only for the base-case scenarios. The summary results of the PSA, which includes the mean total costs, mean total QALYs and the resultant ICERs for GT1a, GT1b and GT4 populations (stratified based on their treatment experience and presence of cirrhosis) are given in Table 5.26, Table 5.27 and Table 5.28, respectively, followed by corresponding CEACs (Figure 5.2, Figure 5.3 and Figure 5.4 respectively). Note that in each subgroup analysis, 1,000 iterations were taken.

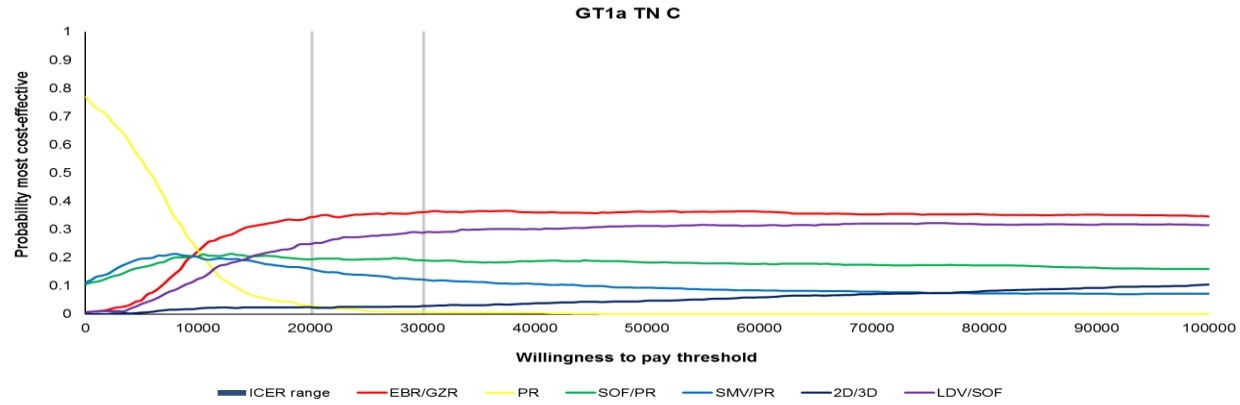
From the CEACs, it could be observed that EBR/GZR becomes the most cost effective intervention in many subgroups. In the GT1a TN C and GT4 TN C populations, EBR/GZR becomes the most cost effective treatment option after a £15,000 per QALY threshold, whereas in the GT1a TE C, and GT4 TE C populations, it becomes the most cost effective after £20,000 per QALY. For GT1b TN C, GT1b TE C and GT1b TE NC populations, EBR/GZR becomes the most cost effective after £40,000, £15,000 and £20,000 per QALY thresholds, respectively. In all other populations, EBR/GZR was never the most cost effective treatment option no matter how high the threshold is set (up to £100,000 per QALY gained).

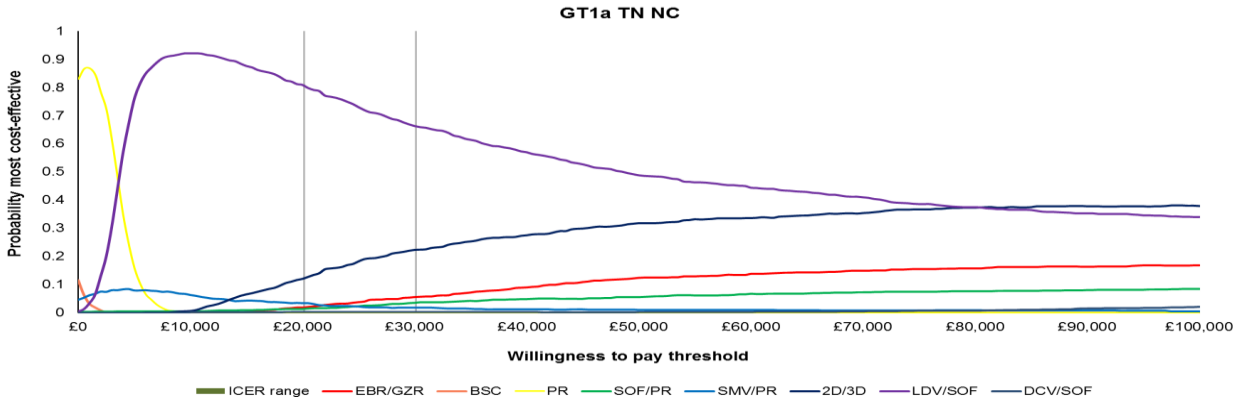
Table 5.26: PSA results for GT1a (TN/TE; NC/C)

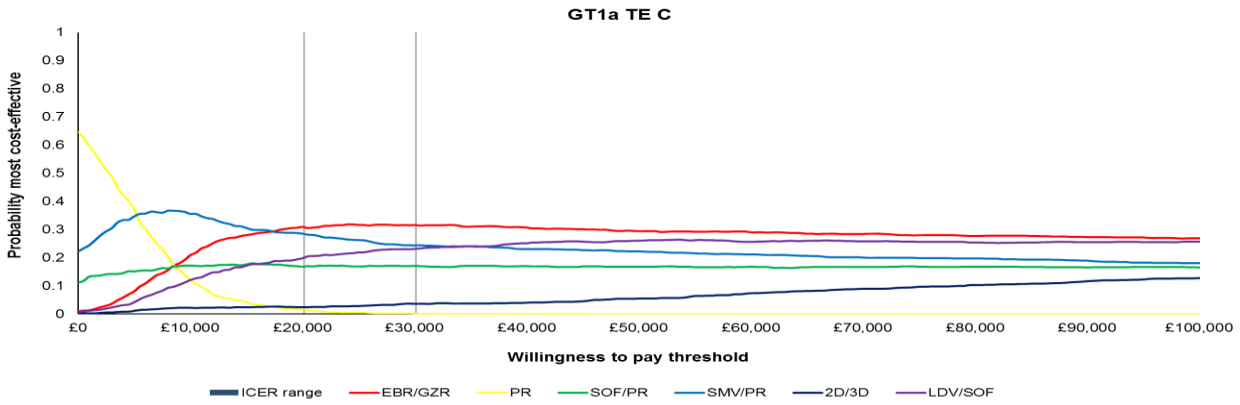
GT1a TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,439	7.768	-	-	-
SMV/PR	£63,871	8.516	£9,432	0.748	£12,604
SOF/PR	£68,033	8.723	£13,595	0.956	£14,228
EBR/GZR	£68,852	9.271	£14,413	1.503	£9,587
LDV/SOF	£70,587	9.264	£16,148	1.497	£10,791
2D/3D	£96,377	9.170	£41,938	1.403	£29,900
GT1a TN NC Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£ 26,627	13.477	-	-	-
BSC	£ 30,406	11.415	£ 3,779	-2.063	Dominated
LDV/SOF	£ 32,259	15.084	£ 5,632	1.606	£3,507
SMV/PR	£ 35,537	14.550	£ 8,910	1.072	£8,311
2D/3D	£ 40,469	15.211	£ 13,842	1.734	£7,983
EBR/GZR	£ 42,335	15.154	£ 15,708	1.677	£9,367
SOF/PR	£ 43,654	14.896	£ 17,027	1.418	£12,005
DCV/SOF	£ 64,903	15.169	£ 38,277	1.691	£22,629
GT1a TE C Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£ 54,596	7.467	-	-	-
SMV/PR	£ 61,805	8.525	£ 7,208	1.058	£6,814
EBR/GZR	£ 67,223	9.123	£ 12,627	1.656	£7,625
SOF/PR	£ 68,552	8.433	£ 13,956	0.966	£14,440
LDV/SOF	£ 69,633	9.068	£ 15,037	1.601	£9,394
2D/3D	£ 95,656	9.004	£ 41,060	1.537	£26,718
GT1a TE NC Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£ 27,674	12.816	-	-	-
BSC	£ 28,899	11.280	£ 1,225	-1.536	Dominated
SMV/PR	£ 34,540	14.177	£ 6,866	1.361	£5,045
2D/3D	£ 40,329	14.645	£ 12,655	1.829	£6,919
EBR/GZR	£ 42,265	14.582	£ 14,592	1.766	£8,264
LDV/SOF	£ 44,130	14.661	£ 16,456	1.845	£8,919
SOF/PR	£ 44,907	14.190	£ 17,233	1.374	£12,541
DCV+SOF	£ 65,099	14.552	£ 37,426	1.736	£21,554

Abbreviations:.ICER:incremental cost-effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

Figure 5.2: Cost effectiveness acceptability curves – GT1a populations







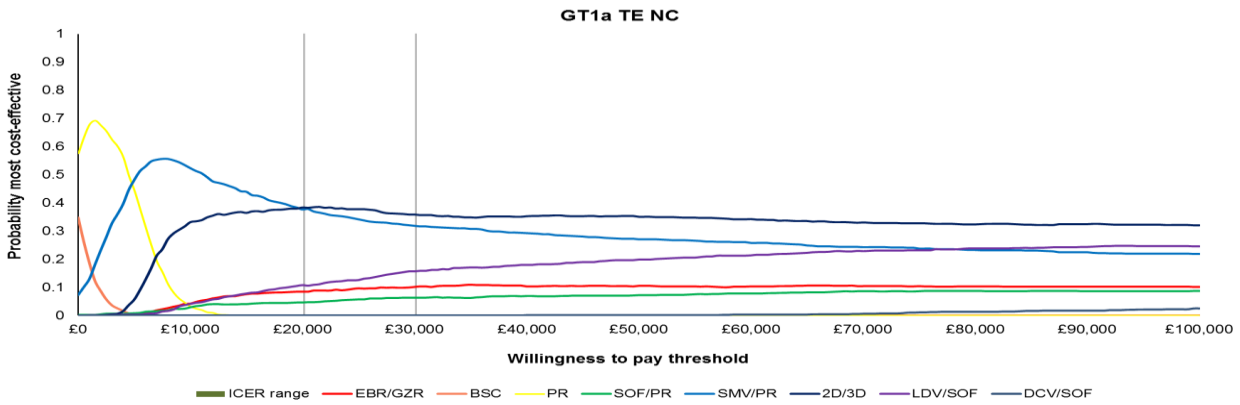


Table 5.27: PSA results for GT1b (TN/TE; NC/C)

GT1b TN C **Technologies**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£ 54,586	7.756	-	-	-
SMV	£ 64,438	8.504	£ 9,853	0.748	£13,170
2D/3D	£ 64,550	9.262	£ 9,964	1.506	£6,615
SOF	£ 66,361	8.926	£ 11,775	1.170	£10,064
EBR/GZR	£ 67,726	9.388	£ 13,140	1.632	£8,051
LDV/SOF	£ 70,406	9.328	£ 15,821	1.572	£10,062
GT1b TN NC **Technologies**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£ 26,798	13.458	-	-	-
BSC	£ 30,326	11.421	£ 3,528	-2.037	Dominated
LDV/SOF	£ 32,196	15.074	£ 5,399	1.616	£3,340
SMV/PR	£ 35,982	14.500	£ 9,184	1.043	£8,808
2D/3D	£ 40,292	15.237	£ 13,495	1.779	£7,585
SOF/PR	£ 41,963	15.159	£ 15,165	1.702	£8,912
EBR/GZR	£ 41,940	15.216	£ 15,142	1.759	£8,609
DCV/SOF	£ 65,425	15.076	£ 38,628	1.619	£23,860
GT1b TE C **Technologies**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£ 53,777	7.646	-	-	-
SMV/PR	£ 60,820	8.641	£ 7,043	0.996	£7,074
2D/3D	£ 64,381	8.970	£ 10,605	1.324	£8,010
EBR/GZR	£ 65,235	9.365	£ 11,459	1.719	£6,667
LDV/SOF	£ 68,304	9.229	£ 14,528	1.583	£9,175
SOF/PR	£ 68,730	8.379	£ 14,954	0.733	£20,400
GT1b TE NC **Technologies**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£ 28,242	12.730	-	-	-
BSC	£ 28,838	11.298	£ 597	-1.432	Dominated
SMV/PR	£ 35,017	14.038	£ 6,775	1.308	£5,180
2D/3D	£ 39,682	14.732	£ 11,440	2.002	£5,714
EBR/GZR	£ 40,602	14.805	£ 12,361	2.075	£5,956
LDV/SOF	£ 43,425	14.749	£ 15,183	2.019	£7,521
SOF/PR	£ 44,666	14.181	£ 16,425	1.451	£11,318
DCV/SOF	£ 64,820	14.584	£ 36,578	1.854	£19,726

Abbreviations:.ICER:incremental cost-effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

Figure 5.3: Cost effectiveness acceptability curves – GT1b populations

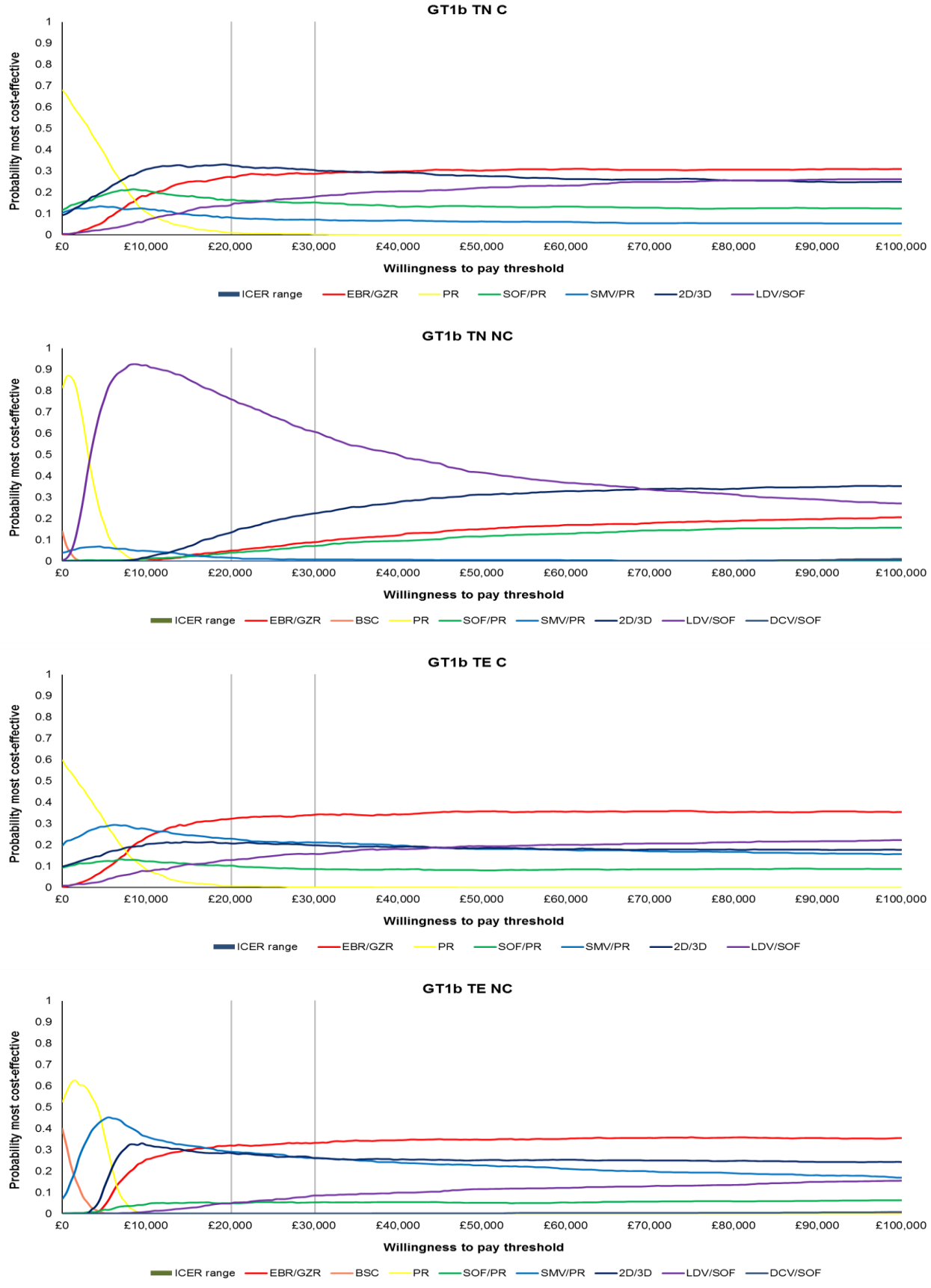
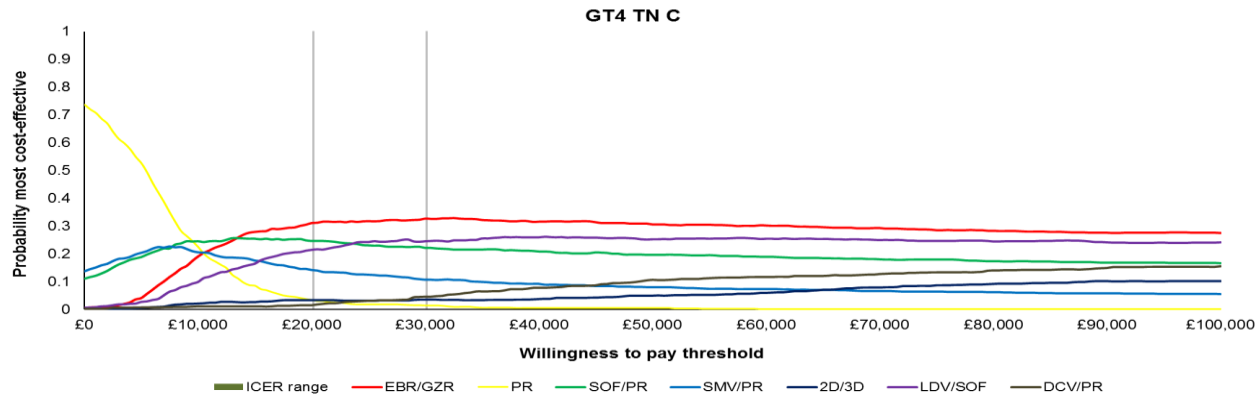


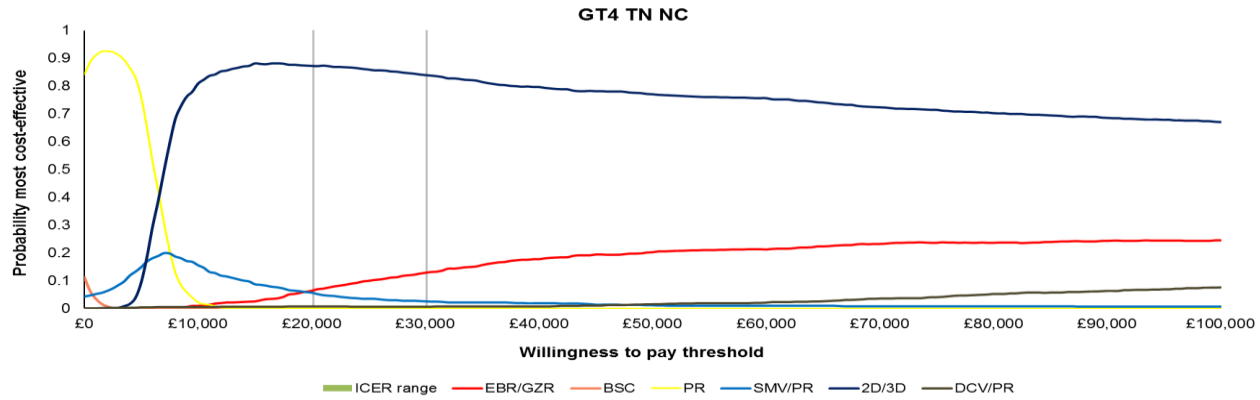
Table 5.28: PSA results for GT4 (TN/TE; NC/C)

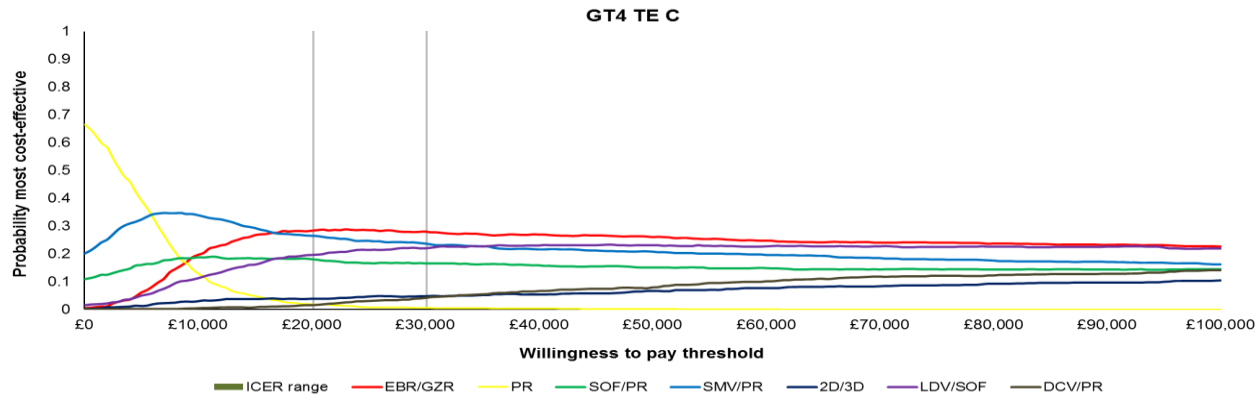
GT4 TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£ 54,262	7.784	-	-	-
SMV/PR	£ 63,721	8.529	£ 9,459	0.745	£12,697
SOF/PR	£ 67,389	8.919	£ 13,127	1.135	£11,563
EBR/GZR	£ 68,610	9.290	£ 14,348	1.507	£9,524
LDV/SOF	£ 70,664	9.259	£ 16,403	1.475	£11,118
DCV/PR	£ 84,303	9.296	£ 30,041	1.512	£19,870
2D/3D	£ 92,284	9.229	£ 38,022	1.445	£26,316
GT4 TN NC **Technologies**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£ 26,616	13.470	-	-	-
BSC	£ 30,411	11.403	£ 3,795	-2.067	Dominated
SMV/PR	£ 35,604	14.573	£ 8,987	1.103	£8,151
2D/3D	£ 37,874	15.216	£ 11,258	1.745	£6,450
EBR/GZR	£ 42,356	15.152	£ 15,739	1.681	£9,362
DCV/PR	£ 58,261	15.162	£ 31,645	1.691	£18,713
GT4 TE C **Technologies**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£ 54,299	7.561	-	-	-
SMV/PR	£ 61,623	8.538	£ 7,324	0.977	£7,495
EBR/GZR	£ 67,144	9.129	£ 12,845	1.568	£8,192
SOF/PR	£ 68,146	8.489	£ 13,847	0.928	£14,922
LDV/SOF	£ 69,386	9.079	£ 15,087	1.518	£9,940
DCV/PR	£ 83,232	9.121	£ 28,933	1.560	£18,545
2D/3D	£ 91,283	8.979	£ 36,984	1.418	£26,088
GT4 TE NC **Technologies**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£ per QALY gained)**
PR	£ 27,687	12.835	-	-	-
BSC	£ 28,896	11.298	£ 1,208	-1.537	Dominated
SMV/PR	£ 34,103	14.172	£ 6,416	1.336	£4,801
2D/3D	£ 37,779	14.643	£ 10,091	1.808	£5,582
EBR/GZR	£ 42,275	14.578	£ 14,588	1.742	£8,372
LDV/SOF	£ 44,050	14.652	£ 16,362	1.816	£9,008
DCV/PR	£ 58,259	14.560	£ 30,571	1.725	£17,722
DCV/SOF	£ 65,101	14.556	£ 37,414	1.720	£21,746

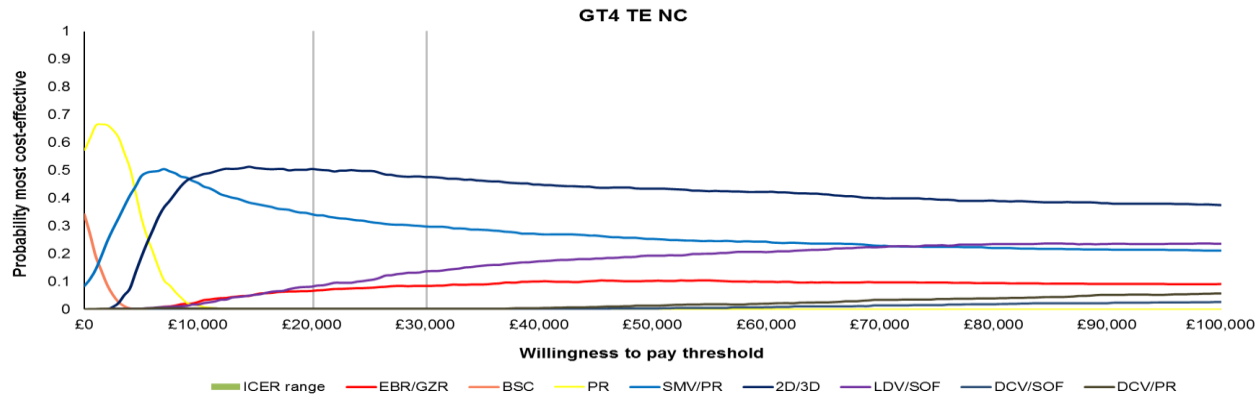
Abbreviations:.ICER:incremental cost-effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

Figure 5.4: Cost effectiveness acceptability curves – GT4 populations









5.2.10.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted for the following key variables using 5% and 95% confidence intervals for the variables except when it is indicated otherwise:

- Cohort characteristics
  - Age (TN:30 and 50, TE:35 and 55)
  - Proportion of male (65% and 75%)
  - Baseline distribution to METAVIR fibrosis stages
  - Proportion of patients re-infected per year
  - Proportion of patients chronically infected following re-infection
- Transition probabilities
- Treatment characteristics
  - SVR rates
  - Discontinuation rate
  - AE rates
- Costs
  - Drug costs
  - Monitoring costs
  - Health state costs
  - AE costs
- Utilities
  - On-treatment utility decrements
  - Health state utilities
- Discount rates (0% and 6%)

The results of the deterministic sensitivity analyses for pairwise comparisons of EBR/GZR and PR were presented in the CS with the help of the tornado diagrams. The deterministic sensitivity analysis revealed that the following inputs appeared to be the most influential inputs on the net monetary benefit of EBR/GZR vs PR with a willingness to pay threshold of £20,000 for all 12 considered subpopulations.

- Discount rate for utility
- Utility of the F4 state
- Discount rate for costs
- Starting age
- Drug cost for EBR/GZR
- SVR of EBR/GZR
- RR of the SVR of PR

ERG comment: The ERG agrees with the approach used for the deterministic sensitivity analyses. However, the discount rates are not subject to parameter uncertainty and thus their impact on the ICER is of no relevance in the current context.

In the CS, only the tornado diagrams are shown for the comparison of EBR/GZR versus PR. However, the electronic model also shows results for all other comparators.

From these tornado diagrams it can be seen that in general, the relative risk of a comparator for SVR shows a large impact on the outcome, as well as the costs of both the comparator drug costs and the EBR/GZR drug costs. In addition, regardless of the comparator, in most cirrhotic subgroups the utility of F4 has a large impact on the ICER whilst in the non-cirrhotic subgroups the starting age is quite influential.

5.2.10.3 Scenario analyses

Several scenario analyses were conducted to explore the structural uncertainties in the economic evaluation. The scenario analyses conducted in the CS are listed as below:

1. Scenario analysis 1 – use of GT4 specific clinical data instead of applying GT1 data to GT4 in the base case: GT4 population specific NMA results for SVR (can be found in Table 5.8), AEs (Table 5.14) and discontinuation rates (Table 5.11) were used for GT4 subgroups for EBR/GZR and comparators when available. (only for GT4 population)
2. Scenario analysis 2 – use of naïve indirect comparison results instead of NMA results in the base case: instead of the NMA results used in the base case, results from naïve indirect comparison for SVR (can be found in Table 5.7), AEs (can be found in Table 5.13) and discontinuation rates (can be found in Table 5.10) were used for EBR/GZR and comparators when available.
3. Scenario analysis 3 – Using age-dependent transition probabilities across fibrosis health states instead of using age-independent transition probabilities in the base case: in this scenario, probabilities from Grishchenko et al., 2009[72] were used instead of the transition probabilities from Thein et al, 2008[93] in the base case. In Grishchenko et al., 2009, fibrosis progression rates differed by age, e.g. differing probabilities for [30-39] versus [40-49] versus [50-59] years old (see Table 5.29).
4. Scenario analysis 4 – Using SVR related utility increments based on European patients from the EBR/GZR clinical trials (0.03) instead of the SVR related utility increment estimate from Wright et al., 2006 (0.05)[67] used in the base-case.
5. Scenario analysis 5 – Implementing probability of transition from "SVR,F4" state to "SVR,F0-F3" state based on the D'Ambrosio (probability=0.167)[113] instead of not having a regression from SVR,F4 states in the base-case.
6. Scenario analysis 6 – Different time horizons
    a. Time horizon of five years instead of life time
    b. Time horizon of 10 years instead of life time

Table 5.29. Age based fibrosis progression probabilities used in scenario analysis 3

	Mean value per age range			Source
	[30-39]	[40-49]	[50-59]	
Non-GT1				
F0 to F1	0.015	0.023	0.035	Grishchenko et al., 2009[72]
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	
GT1				
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	

Abbreviations: GT1: genotype 1; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, compensated cirrhosis.

In almost all subgroups, ICERs of all treatments (except for BSC) increased extensively compared to PR for shorter time horizons. This was expected since the savings from better health states are spread to further years, whereas the drug acquisition costs are invested in the first year.

Among the other scenarios, scenario 3 did not have any effect on patients with cirrhosis, since transition probabilities for the progression in-between F0-F3 and to F4 states would not affect cirrhotic patients who are at F4 at baseline. However, for all non-cirrhotic patient populations, using the age-specific probabilities from Grishchenko et al., 2009[72] had a substantial impact on the ICER (vs PR) for all the interventions. For all interventions, ICERs increased 100% to 200% compared to the base-case ICER.

Incorporating possible transitions from "SVR, F4" to "SVR, F0-F3" states resulted in considerably favourable results in terms of ICER compared to base-case for cirrhotic patient populations. This change was expected since there are more patients in SVR states in EBR/GZR and other DAA-including regimens compared to PR, and the health state cost and utilities of the "SVR, F0-F3" states are more favourable than "SVR, F4". For non-cirrhotic patient populations, this scenario (scenario 5) did not affect the incremental results.

Using the SVR utility increment of (0.03) instead of the SVR related utility increment estimate from Wright et al., 2006 (0.05)[67] had an impact on incremental QALYS, and in this scenario (scenario 4), ICER of the interventions have increased around £1,000 per QALY gained in general.

Using GT4 specific data (scenario 1) or using naïve indirect NMA results (scenario 2) have substantial effects on the ICER results. However, there is no unidirectional trend for the ICER changes in these scenarios in between populations and treatments. Therefore, besides acknowledging the presence of the important effects, it is not possible to make any judgements on the direction of the effect of the scenarios 1 and 2 (choice of treatment input effectiveness data) on the ICER values.

Note that scenario 1 was only relevant for GT4 populations, therefore it is not listed in the tables presenting results from GT1a and GT1b populations. Furthermore, if there is an asterisk sign (*) next to the reported ICER value, it means that the corresponding intervention's ICER lies in the southwest quadrant, hence the intervention results in less total costs and less total QALYs.

Table 5.30: Incremental costs, QALYs and ICERs for each comparator - GT1a TN C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£10,781	0.714	£15,095	£10,308	1.104	£9,338	£16,342	1.518	£10,765
Scenario 2	£12,234	0.650	£18,822	£16,376	1.104	£14,838	£15,926	1.556	£10,233
Scenario 3	£10,781	0.714	£15,095	£10,308	1.104	£9,338	£16,342	1.518	£10,765
Scenario 4	£10,781	0.634	£16,992	£10,308	0.974	£10,584	£16,342	1.347	£12,128
Scenario 5	£6,705	1.606	£4,175	£3,665	2.558	£1,433	£7,621	3.428	£2,223
Scenario 6a	£15,226	0.134	£113,537	£17,365	0.191	£90,942	£25,479	0.259	£98,191
Scenario 6b	£13,212	0.232	£56,986	£14,138	0.341	£41,517	£21,174	0.469	£45,119
	EBR/GZR vs. PR			2D/3D vs. PR					
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER			
Base case	£13,956	1.518	£9,193	£42,166	1.467	£28,742			
Scenario 2	£13,639	1.531	£8,906	£47,800	1.513	£31,584			
Scenario 3	£13,956	1.518	£9,193	£42,166	1.467	£28,742			
Scenario 4	£13,956	1.348	£10,357	£42,166	1.308	£32,228			
Scenario 5	£5,236	3.428	£1,527	£34,057	3.243	£10,503			
Scenario 6a	£23,094	0.259	£89,002	£50,736	0.247	£205,703			
Scenario 6b	£18,789	0.469	£40,033	£46,651	0.453	£103,054			

Table 5.31: Incremental costs, QALYs and ICERs for each comparator -GT1a TN NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£3,932	-2.069	Dominated	£10,113	1.077	£9,388	£17,275	1.469	£11,762
Scenario 2	£3,584	-2.030	Dominated	£9,231	1.222	£7,554	£16,084	1.647	£9,768
Scenario 3	-£1,896	-1.072	£1,768*	£13,055	0.569	£22,945	£21,424	0.753	£28,466
Scenario 4	£3,932	-1.890	Dominated	£10,113	0.974	£10,382	£17,275	1.323	£13,062
Scenario 5	£3,932	-2.069	Dominated	£10,113	1.077	£9,388	£17,275	1.469	£11,763
Scenario 6a	-£9,065	-0.046	£195,903*	£17,104	0.149	£114,583	£27,087	0.190	£142,655
Scenario 6b	-£6,800	-0.262	£25,933*	£16,040	0.257	£62,324	£25,576	0.334	£76,484
	LDV/SOF vs. PR			EBR/GZR vs. PR			DCV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£5,479	1.625	£3,371	£15,809	1.677	£9,427	£38,321	1.744	£21,976
Scenario 2	£5,396	1.629	£3,313	£15,460	1.716	£9,008	£38,013	1.783	£21,317
Scenario 3	£10,014	0.843	£11,881	£20,452	0.876	£23,347	£43,176	0.907	£47,628
Scenario 4	£5,479	1.465	£3,739	£15,809	1.515	£10,438	£38,321	1.574	£24,340
Scenario 5	£5,479	1.625	£3,371	£15,809	1.677	£9,427	£38,321	1.744	£21,976
Scenario 6a	£16,186	0.236	£68,532	£26,759	0.236	£113,422	£49,759	0.233	£213,104
Scenario 6b	£14,530	0.392	£37,033	£25,062	0.398	£62,991	£47,983	0.403	£119,097
	2D/3D vs. PR								
	Incr. Costs	Incr. QALYs	ICER						
Base case	£13,899	1.752	£7,935						
Scenario 2	£13,889	1.753	£7,921						
Scenario 3	£18,754	0.914	£20,509						
Scenario 4	£13,899	1.582	£8,784						
Scenario 5	£13,899	1.752	£7,935						
Scenario 6a	£25,337	0.242	£104,886						
Scenario 6b	£23,561	0.411	£57,334						

Table 5.32: Incremental costs, QALYs and ICERs for each comparator - GT1a TE C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£6,504	1.145	£5,681	£10,252	1.066	£9,616	£14,292	1.692	£8,448
Scenario 2	£7,428	1.141	£6,507	£16,639	1.031	£16,132	£15,167	1.586	£9,563
Scenario 3	£6,504	1.145	£5,681	£10,252	1.066	£9,616	£14,292	1.692	£8,448
Scenario 4	£6,504	1.016	£6,400	£10,252	0.940	£10,903	£14,292	1.503	£9,512
Scenario 5	£128	2.502	£51	£4,009	2.395	£1,674	£4,903	3.691	£1,328
Scenario 6a	£13,859	0.176	£78,551	£17,511	0.196	£89,414	£24,904	0.290	£85,775
Scenario 6b	£10,438	0.343	£30,403	£14,255	0.341	£41,767	£19,938	0.531	£37,547
	EBR/GZR vs. PR			2D/3D vs. PR					
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER			
Base case	£12,113	1.669	£7,257	£39,504	1.713	£23,062			
Scenario 2	£12,868	1.563	£8,233	£45,568	1.711	£26,628			
Scenario 3	£12,113	1.669	£7,257	£39,504	1.713	£23,062			
Scenario 4	£12,113	1.482	£8,172	£39,504	1.528	£25,858			
Scenario 5	£2,848	3.642	£782	£30,315	3.669	£8,262			
Scenario 6a	£22,592	0.288	£78,538	£49,933	0.285	£175,130			
Scenario 6b	£17,693	0.525	£33,716	£44,987	0.532	£84,494			

Table 5.33: Incremental costs, QALYs and ICERs for each comparator - GT1a TE NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£999	-1.535	Dominated	£7,146	1.398	£5,112	£17,275	1.393	£12,403
Scenario 2	£340	-1.456	Dominated	£7,085	1.428	£4,962	£17,346	1.397	£12,421
Scenario 3	-£3,395	-0.812	£4,180*	£11,214	0.725	£15,477	£21,394	0.711	£30,095
Scenario 4	£999	-1.400	Dominated	£7,146	1.257	£5,685	£17,275	1.247	£13,848
Scenario 5	£999	-1.535	Dominated	£7,146	1.398	£5,112	£17,275	1.393	£12,403
Scenario 6a	-£8,630	-0.007	£1,212,681*	£16,778	0.174	£96,401	£27,061	0.202	£134,012
Scenario 6b	-£6,759	-0.186	£36,301*	£15,184	0.324	£46,843	£25,452	0.348	£73,043
	LDV/SOF vs. PR			EBR/GZR vs. PR			DCV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£15,911	1.907	£8,343	£14,462	1.773	£8,159	£36,763	1.864	£19,718
Scenario 2	£15,239	1.986	£7,673	£13,804	1.851	£7,455	£34,964	2.100	£16,650
Scenario 3	£21,435	0.994	£21,571	£19,592	0.924	£21,207	£42,185	0.968	£43,594
Scenario 4	£15,911	1.715	£9,276	£14,462	1.594	£9,075	£36,763	1.676	£21,936
Scenario 5	£15,911	1.907	£8,343	£14,462	1.773	£8,159	£36,763	1.864	£19,718
Scenario 6a	£28,928	0.274	£105,518	£26,575	0.263	£100,983	£49,547	0.263	£188,192
Scenario 6b	£26,751	0.473	£56,563	£24,556	0.447	£54,895	£47,411	0.458	£103,449
	2D/3D vs. PR								
	Incr. Costs	Incr. QALYs	ICER						
Base case	£12,079	1.907	£6,334						
Scenario 2	£11,217	2.022	£5,549						
Scenario 3	£17,602	0.994	£17,716						
Scenario 4	£12,079	1.715	£7,042						
Scenario 5	£12,079	1.907	£6,334						
Scenario 6a	£25,096	0.274	£91,530						
Scenario 6b	£22,918	0.473	£48,458						

Table 5.34: Incremental costs, QALYs and ICERs for each comparator - GT1b TN C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£10,687	0.725	£14,741	£7,743	1.398	£5,538	£15,436	1.622	£9,517
Scenario 2	£12,349	0.637	£19,394	£13,996	1.377	£10,166	£16,001	1.548	£10,338
Scenario 3	£10,687	0.725	£14,741	£7,743	1.398	£5,538	£15,436	1.622	£9,517
Scenario 4	£10,687	0.644	£16,593	£7,743	1.236	£6,264	£15,436	1.440	£10,719
Scenario 5	£6,551	1.630	£4,019	-£540	3.212	Dominant	£6,135	3.659	£1,677
Scenario 6a	£15,202	0.135	£112,678	£16,446	0.224	£73,412	£25,166	0.271	£92,962
Scenario 6b	£13,155	0.234	£56,168	£12,383	0.418	£29,597	£20,562	0.496	£41,436
	EBR/GZR vs. PR			2D/3D vs. PR					
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER			
Base case	£12,829	1.647	£7,787	£10,062	1.618	£6,217			
Scenario 2	£12,846	1.622	£7,918	£11,623	1.622	£7,166			
Scenario 3	£12,829	1.647	£7,787	£10,062	1.618	£6,217			
Scenario 4	£12,829	1.463	£8,771	£10,062	1.436	£7,005			
Scenario 5	£3,388	3.715	£912	£755	3.657	£206			
Scenario 6a	£22,701	0.274	£82,981	£19,795	0.271	£73,038			
Scenario 6b	£18,025	0.503	£35,836	£15,195	0.496	£30,655			

Table 5.35: Incremental costs, QALYs and ICERs for each comparator -GT1b TN NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£3,712	-2.039	Dominated	£10,262	1.057	£9,710	£15,361	1.733	£8,865
Scenario 2	£3,447	-2.011	Dominated	£9,312	1.211	£7,691	£15,256	1.761	£8,665
Scenario 3	-£2,030	-1.056	£1,922*	£13,146	0.558	£23,541	£20,256	0.889	£22,797
Scenario 4	£3,712	-1.862	Dominated	£10,262	0.956	£10,740	£15,361	1.562	£9,834
Scenario 5	£3,713	-2.039	Dominated	£10,262	1.057	£9,710	£15,361	1.733	£8,865
Scenario 6a	-£9,084	-0.044	£204,799*	£17,120	0.148	£116,016	£26,895	0.209	£128,492
Scenario 6b	-£6,850	-0.257	£26,616*	£16,079	0.254	£63,406	£25,105	0.380	£66,069
	LDV/SOF vs. PR			EBR/GZR vs. PR			DCV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£5,099	1.678	£3,039	£15,162	1.766	£8,585	£38,218	1.758	£21,739
Scenario 2	£4,035	1.817	£2,221	£14,896	1.794	£8,303	£37,516	1.852	£20,259
Scenario 3	£9,782	0.870	£11,246	£20,058	0.922	£21,757	£43,113	0.914	£47,176
Scenario 4	£5,099	1.513	£3,370	£15,162	1.595	£9,504	£38,218	1.587	£24,076
Scenario 5	£5,099	1.678	£3,039	£15,162	1.766	£8,585	£38,218	1.758	£21,739
Scenario 6a	£16,150	0.240	£67,354	£26,697	0.242	£110,203	£49,752	0.234	£212,426
Scenario 6b	£14,440	0.401	£36,001	£24,907	0.413	£60,310	£47,962	0.405	£118,444
	2D/3D vs. PR								
	Incr. Costs	Incr. QALYs	ICER						
Base case	£13,432	1.804	£7,446						
Scenario 2	£12,970	1.860	£6,974						
Scenario 3	£18,433	0.941	£19,582						
Scenario 4	£13,432	1.630	£8,242						
Scenario 5	£13,432	1.804	£7,446						
Scenario 6a	£25,211	0.245	£102,875						
Scenario 6b	£23,381	0.420	£55,730						

Table 5.36: Incremental costs, QALYs and ICERs for each comparator - GT1b TE C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£5,751	1.229	£4,680	£12,769	0.786	£16,253	£13,681	1.760	£7,773
Scenario 2	£7,745	1.106	£7,001	£21,355	0.506	£42,208	£15,483	1.551	£9,984
Scenario 3	£5,751	1.229	£4,680	£12,769	0.786	£16,253	£13,681	1.760	£7,773
Scenario 4	£5,751	1.091	£5,271	£12,769	0.690	£18,500	£13,681	1.563	£8,751
Scenario 5	-£1,077	2.682	Dominant	£8,037	1.793	£4,482	£3,925	3.837	£1,023
Scenario 6a	£13,565	0.187	£72,483	£18,366	0.165	£111,153	£24,632	0.300	£81,997
Scenario 6b	£9,909	0.367	£26,963	£15,937	0.267	£59,672	£19,485	0.552	£35,281
	EBR/GZR vs. PR			2D/3D vs. PR					
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER			
Base case	£11,296	1.760	£6,418	£8,746	1.708	£5,122			
Scenario 2	£11,320	1.736	£6,522	£10,536	1.686	£6,248			
Scenario 3	£11,296	1.760	£6,418	£8,746	1.708	£5,122			
Scenario 4	£11,296	1.563	£7,225	£8,746	1.516	£5,769			
Scenario 5	£1,540	3.837	£401	-£753	3.730	Dominant			
Scenario 6a	£22,247	0.300	£74,060	£19,418	0.295	£65,809			
Scenario 6b	£17,099	0.552	£30,960	£14,417	0.538	£26,775			

Table 5.37: Incremental costs, QALYs and ICERs for each comparator - GT1b TE NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£428	-1.459	Dominated	£6,770	1.448	£4,676	£15,987	1.564	£10,225
Scenario 2	£530	-1.481	Dominated	£6,922	1.449	£4,776	£16,250	1.542	£10,540
Scenario 3	-£3,745	-0.773	£4,845*	£10,984	0.750	£14,637	£20,604	0.799	£25,775
Scenario 4	£428	-1.332	Dominated	£6,770	1.302	£5,199	£15,987	1.402	£11,406
Scenario 5	£428	-1.459	Dominated	£6,770	1.448	£4,676	£15,987	1.564	£10,225
Scenario 6a	-£8,682	-0.002	£4,552,946*	£16,746	0.177	£94,474	£26,930	0.215	£125,310
Scenario 6b	-£6,898	-0.173	£39,873*	£15,095	0.333	£45,391	£25,121	0.380	£66,157
	LDV/SOF vs. PR			EBR/GZR vs. PR			DCV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£14,654	2.074	£7,066	£12,188	2.074	£5,877	£35,244	2.066	£17,060
Scenario 2	£15,000	2.018	£7,434	£12,290	2.052	£5,989	£35,154	2.075	£16,944
Scenario 3	£20,663	1.080	£19,131	£18,198	1.080	£16,848	£41,253	1.072	£38,479
Scenario 4	£14,654	1.866	£7,854	£12,188	1.866	£6,532	£35,244	1.858	£18,970
Scenario 5	£14,654	2.074	£7,066	£12,188	2.074	£5,877	£35,244	2.066	£17,060
Scenario 6a	£28,800	0.287	£100,421	£26,335	0.287	£91,824	£49,390	0.279	£177,182
Scenario 6b	£26,428	0.503	£52,496	£23,963	0.503	£47,598	£47,018	0.495	£94,910
	2D/3D vs. PR								
	Incr. Costs	Incr. QALYs	ICER						
Base case	£10,499	2.105	£4,988						
Scenario 2	£10,608	2.083	£5,093						
Scenario 3	£16,598	1.096	£15,143						
Scenario 4	£10,499	1.894	£5,544						
Scenario 5	£10,499	2.105	£4,988						
Scenario 6a	£24,852	0.289	£85,905						
Scenario 6b	£22,443	0.509	£44,069						

Table 5.38: Incremental costs, QALYs and ICERs for each comparator – GT4 TN C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£10,781	0.714	£15,095	£8,802	1.277	£6,894	£16,342	1.518	£10,765
Scenario 1	£6,801	1.595	£4,265	£2,958	1.760	£1,681	£14,724	2.054	£7,167
Scenario 2	£12,234	0.650	£18,822	£14,719	1.294	£11,377	£15,926	1.556	£10,233
Scenario 3	£10,781	0.714	£15,095	£8,802	1.277	£6,894	£16,342	1.518	£10,765
Scenario 4	£10,781	0.634	£16,992	£8,802	1.128	£7,804	£16,342	1.347	£12,128
Scenario 5	£6,705	1.606	£4,175	£1,196	2.942	£406	£7,621	3.428	£2,223
Scenario 6a	£15,226	0.134	£113,537	£16,818	0.211	£79,815	£25,479	0.259	£98,191
Scenario 6b	£13,212	0.232	£56,986	£13,102	0.387	£33,885	£21,174	0.469	£45,119
	EBR/GZR vs. PR			DCV/PR vs. PR			2D/3D vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£13,956	1.518	£9,193	£29,750	1.560	£19,076	£38,734	1.541	£25,138
Scenario 1	£11,547	2.053	£5,623	£13,685	1.518	£9,017	£26,582	2.034	£13,069
Scenario 2	£13,639	1.531	£8,906	£29,219	1.599	£18,279	£41,745	1.585	£26,340
Scenario 3	£13,956	1.518	£9,193	£29,750	1.560	£19,076	£38,734	1.541	£25,138
Scenario 4	£13,956	1.348	£10,357	£29,750	1.386	£21,471	£38,734	1.375	£28,176
Scenario 5	£5,236	3.428	£1,527	£20,860	3.506	£5,949	£30,242	3.400	£8,894
Scenario 6a	£23,094	0.259	£89,002	£39,136	0.199	£196,878	£47,700	0.254	£187,758
Scenario 6b	£18,789	0.469	£40,033	£34,623	0.429	£80,648	£43,409	0.472	£92,048

Table 5.39: Incremental costs, QALYs and ICERs for each comparator -GT4 TN NC

	BSC vs. PR			SMV/PR vs. PR			EBR/GZR vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£3,932	-2.069	Dominated	£10,113	1.077	£9,388	£15,809	1.677	£9,427
Scenario 1	£2,058	-1.647	Dominated	£6,156	1.816	£3,390	£13,809	2.109	£6,549
Scenario 2	£3,584	-2.030	Dominated	£9,231	1.222	£7,554	£15,460	1.716	£9,008
Scenario 3	-£818	-1.249	£655*	£12,507	0.660	£18,959	£19,586	1.019	£19,224
Scenario 4	£3,932	-1.890	Dominated	£10,113	0.974	£10,382	£15,809	1.515	£10,438
Scenario 5	£3,932	-2.069	Dominated	£10,113	1.077	£9,388	£15,809	1.677	£9,427
Scenario 6a	-£9,065	-0.046	£195,903*	£17,104	0.149	£114,583	£26,759	0.236	£113,422
Scenario 6b	-£6,800	-0.262	£25,933*	£16,040	0.257	£62,324	£25,062	0.398	£62,991

	DCV/PR vs. PR			2D/3D vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£31,598	1.735	£18,217	£11,204	1.752	£6,396
Scenario 1	£32,493	1.141	£28,471	£9,673	2.109	£4,588
Scenario 2	£31,005	1.812	£17,108	£10,863	1.791	£6,064
Scenario 3	£35,561	1.045	£34,033	£15,154	1.064	£14,244
Scenario 4	£31,598	1.568	£20,153	£11,204	1.583	£7,080
Scenario 5	£31,598	1.735	£18,217	£11,204	1.752	£6,396
Scenario 6a	£43,054	0.171	£252,046	£22,642	0.242	£93,745
Scenario 6b	£41,275	0.346	£119,175	£20,866	0.411	£50,778

Table 5.40: Incremental costs, QALYs and ICERs for each comparator – GT4 TE C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£6,760	1.116	£6,055	£10,875	0.997	£10,911	£14,916	1.622	£9,194
Scenario 1	£16,382	0.472	£34,717	£9,304	1.007	£9,241	£16,435	1.810	£9,078
Scenario 2	£7,428	1.141	£6,507	£16,639	1.031	£16,132	£15,167	1.586	£9,563
Scenario 3	£6,760	1.116	£6,055	£10,875	0.997	£10,911	£14,916	1.622	£9,194
Scenario 4	£6,760	0.991	£6,821	£10,875	0.878	£12,381	£14,916	1.441	£10,353
Scenario 5	£537	2.441	£220	£5,006	2.246	£2,229	£5,901	3.542	£1,666
Scenario 6a	£13,927	0.174	£80,019	£17,706	0.189	£93,720	£25,099	0.283	£88,557
Scenario 6b	£10,596	0.337	£31,471	£14,660	0.324	£45,284	£20,343	0.513	£39,620
	EBR/GZR vs. PR			DCV/PR vs. PR			2D/3D vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£12,736	1.600	£7,962	£28,343	1.662	£17,054	£37,306	1.647	£22,645
Scenario 1	£20,720	0.978	£21,192	£12,006	1.667	£7,204	£28,299	1.791	£15,797
Scenario 2	£12,868	1.563	£8,233	£27,352	1.752	£15,614	£40,135	1.712	£23,450
Scenario 3	£12,736	1.600	£7,962	£28,343	1.662	£17,054	£37,306	1.647	£22,645
Scenario 4	£12,736	1.420	£8,967	£28,343	1.477	£19,189	£28,343	1.477	£19,189
Scenario 5	£3,845	3.493	£1,101	£19,172	3.614	£5,305	£28,498	3.523	£8,090
Scenario 6a	£22,788	0.281	£81,168	£38,743	0.222	£174,130	£47,302	0.278	£170,127
Scenario 6b	£18,098	0.507	£35,682	£33,789	0.473	£71,489	£42,561	0.516	£82,549

Table 5.41: Incremental costs, QALYs and ICERs for each comparator – GT4 TE NC

	BSC vs. PR			SMV/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£999	-1.535	Dominated	£7,146	1.398	£5,112	£15,911	1.907	£8,343
Scenario 1	£1,539	-1.449	Dominated	£11,037	1.067	£10,347	£15,427	2.114	£7,298
Scenario 2	£340	-1.456	Dominated	£7,085	1.428	£4,962	£15,239	1.986	£7,673
Scenario 3	-£2,599	-0.939	£2,768	£10,472	0.843	£12,419	£20,427	1.155	£17,689
Scenario 4	£999	-1.400	Dominated	£7,146	1.257	£5,685	£15,911	1.715	£9,276
Scenario 5	£999	-1.535	Dominated	£7,146	1.398	£5,112	£15,911	1.907	£8,343
Scenario 6a	-£8,630	-0.007	£1,212,681*	£16,778	0.174	£96,401	£28,928	0.274	£105,518
Scenario 6b	-£6,759	-0.186	£36,301*	£15,184	0.324	£46,843	£26,751	0.473	£56,563
	EBR/GZR vs. PR			DCV/PR vs. PR			DCV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£14,462	1.773	£8,159	£30,037	1.859	£16,160	£36,763	1.864	£19,718
Scenario 1	£13,010	2.114	£6,154	£31,468	1.217	£25,857	£35,699	2.106	£16,952
Scenario 2	£13,804	1.851	£7,455	£28,240	2.093	£13,493	£34,964	2.100	£16,650
Scenario 3	£18,656	1.074	£17,378	£34,482	1.118	£30,832	£41,196	1.126	£36,593
Scenario 4	£14,462	1.594	£9,075	£30,037	1.673	£17,956	£36,763	1.676	£21,936
Scenario 5	£14,462	1.773	£8,159	£30,037	1.859	£16,160	£36,763	1.864	£19,718
Scenario 6a	£26,575	0.263	£100,983	£42,836	0.200	£213,724	£49,547	0.263	£188,192
Scenario 6b	£24,556	0.447	£54,895	£40,694	0.401	£101,442	£47,411	0.458	£103,449
	2D/3D vs. PR								
	Incr. Costs	Incr. QALYs	ICER						
Base case	£9,384	1.907	£4,920						
Scenario 1	£8,875	2.114	£4,198						
Scenario 2	£8,465	2.022	£4,187						
Scenario 3	£13,900	1.155	£12,036						
Scenario 4	£9,384	1.715	£5,471						
Scenario 5	£9,384	1.907	£4,920						
Scenario 6a	£22,401	0.274	£81,714						
Scenario 6b	£20,224	0.473	£42,762						

5.2.11 Model validation and face validity check

In the CS, it was mentioned that the model approach and inputs had been validated by an external health economist with expertise in hepatitis C, who was described as a leading expert in health economics practice and methodology development in the UK for the economic evaluation of HCV. It was also mentioned that the accuracy of the implementation and programming of the model was verified via internal quality control processes using an internal quality control checklist, which was given in Appendix 23 of the CS.[56]

ERG comment: In the CS, no details were given concerning the validation by an external health economist as well as by the clinical experts. The company did not provide these details despite the request of the ERG.[65] Furthermore, the ERG requested the filled in version of the checklist provided in Appendix 23 of the CS,[56] however the company did not provide this either.

There were also no other validation efforts, and the ERG asked the company to conduct additional validation exercises such as cross-validation, validation against external data, validation against internal data. However, in the response to the clarification letter, the company stated (B26[65]): "*MSD believes all necessary validation of the model has been conducted and does not believe that further validation would provide additional value to the model.*"

The ERG disagrees strongly with the company's statement, and thinks that validation efforts suggested in the clarification letter constitute one of the most important part of the company evidence, and not providing any details on the validation is a serious violation of good modelling practice.[114]

The ERG had a quick check with the in-house quality assurance checklist to confirm technical validity of the model and no serious errors were found. The total QALY estimates from the previous TAs (e.g. TA 364)[90] of a common intervention like PR were comparable with those from the CS. However further than this, the ERG cannot make any other conclusive remarks on the validation status of the cost effectiveness evidence submitted by the company.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 ERG base-case analyses

Based on the remarks raised in Section 5.2 of this report, the ERG defined a new base-case analysis. Unfortunately, one issue could not be addressed quantitatively, i.e. the 16 week treatment duration for patients with GT1a and the presence of specific NS5A RAVs causing at least a five-fold reduction in activity of elbasvir. In order to select these patients, all patients would first need a test to assess the presence of any polymorphisms that could impact treatment effectiveness. Thus, for all patients entering the model, the costs of such test should be added.

Once the GT1a patients with polymorphisms have been detected, they will receive 16 weeks of EBR/GZR plus ribavirin instead of the 12 weeks assumed in the current model. Thus, overall treatment costs will go up. At the same time, the number of patients reaching SVR will increase, as the prolonged intervention will lead to a higher overall SVR rate in GT1a patients. This will in turn lead to more life years and more QALYs. At the same time, costs will be saved by having fewer patients in the more severe (and costly) health states. Thus, including testing into the model will have impact on almost every part of the model outcomes, and it is currently not possible to predict what the net effect will be on the cost effectiveness of EBR/GZR. In order to quantify this effect, it would be necessary to have

SVR rates, discontinuation rates and AE rates separated out for patients with a negative test result receiving 12 weeks of treatment and patients with a positive test result receiving 16 weeks of EBR/GZR plus ribavirin.

All other relevant issues discussed in Section 5.2 could be quantified, so a new ERG base-case was defined based on the following adjustments:

- *Model structure adjustment to allow that after reinfection, patients return to the fibrosis stage they had been just before SVR.*

As described in Section 5.2.3, the ERG has the opinion that a modelling approach, in which patients return to the fibrosis stage they were in before reaching SVR, would reflect the clinical prognosis better than the approach followed in CS, in which patients always return to "no fibrosis" (F0) stage, after being re-infected. Therefore, in the ERG base-case, the former approach was selected as the ERG base-case and the latter approach (CS base-case) explored as an ERG scenario analysis.

- *Using SVR related utility increments from the EBR/GZR clinical trials.*

As described in Section 5.2.7, the ERG, believes that the fibrosis health state and SVR related utility increment estimates from Wright et al., 2006,[67] which were used in the company's base-case, may not reflect the current UK clinical practice, since these estimates are older than 10 years. Ideally, the ERG would prefer to use both fibrosis disease stage (F0-F4) utility and SVR related utility increment estimates derived from the EBR/GZR clinical trials. However, the former (fibrosis disease stage utility) estimates were not available to the ERG. The company provided an estimate for the SVR related utility increment based on European patients from the EBR/GZR clinical trials. This estimate (0.03) is a bit lower than the Wright et al., 2006[67] estimate (0.05). Despite the fact that this estimate from the EBR/GZR clinical trials was not derived from UK patients and despite the presence of some methodological issues discussed in Section 5.2.7 (such as not using EQ-5D-5L value sets), the ERG still believes that this would be a more plausible estimate for the SVR related utility increments in the ERG base-case, since it is much more recent. Therefore in the ERG base-case, SVR related utility increments from the EBR/GZR clinical trials were applied, whereas the estimate from Wright et al., 2006 (0.05)[67] is applied in one of the ERG scenarios.

- *Age-based utility decrements were removed from the base-case analyses*

As described in Section 5.2.7, the ERG expressed its concerns on the potential double counting while incorporating the age-based utility decrements in the CS model and on the implementation of decrements as a linear function. Furthermore, the ERG noticed that these age based utility decrements were generally not included in previous STAs, except for TA364[90]. In the ERG base-case, it was decided not to include age-based utility decrements, whereas in one of the ERG scenarios, age-based utility decrements were included.

The ERG decided to keep other assumptions of the base-case analyses from the model submitted by the company.

The ERG base-case pairwise incremental cost effectiveness results for comparisons of EBR/GZR and its relevant comparators versus PR across all the different populations are listed in Table 5.42 for GT1a, in Table 5.43 for GT1b and in Table 5.44 for GT4 patients. Next to the pairwise incremental results, full incremental results are also provided in Tables 5.45 to Tables 5.47.

The findings of the ERG base-case analysis are generally in line with those from the CS. For GT1a and GT4 populations, the ICER (compared to PR) values for EBR/GZR were around £8,000-£9,000

per QALY gained for cirrhosis patients and around £11,000-£12,000 per QALY gained for non-cirrhosis patients. For GT1b, in the TN and NC populations, ICER (compared to PR) was almost £13,000 per QALY gained, whereas for the other GT1b populations, ICER values were around £8,000 per QALY gained.

From the full incremental analysis, EBR/GZR appeared to be cost effective only in GT1a TN C, GT1a TE C and GT4 TE C populations. In GT4 TN C population, EBR/GZR resulted in an ICER around the £20,000 per QALY gained threshold, and in all other populations, EBR/GZR was either dominated by the other cost effective interventions, or the ICER values compared to the other cost effective interventions were above the £20,000 per QALY gained threshold.

Table 5.42: ERG pairwise base-case analyses for GT1a (TN/TE; C/NC), all comparisons against PR

GT1a TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,599	8.423	-	-	-
SOF/PR	£64,907	9.491	£10,308	1.068	£9,647
SMV/PR	£65,380	9.094	£10,781	0.671	£16,071
EBR/GZR	£68,555	9.907	£13,956	1.484	£9,406
LDV/SOF	£70,941	9.907	£16,342	1.484	£11,014
2D/3D	£96,765	9.851	£42,166	1.428	£29,526
GT1a TN NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£27,895	14.280	-	-	-
BSC	£30,513	12.474	£2,617	-1.806	Dominated
LDV/SOF	£34,543	15.618	£6,648	1.338	£4,967
SMV/PR	£38,763	15.150	£10,868	0.871	£12,483
2D/3D	£43,033	15.726	£15,138	1.447	£10,462
EBR/GZR	£44,892	15.663	£16,997	1.383	£12,287
SOF/PR	£46,239	15.481	£18,344	1.201	£15,271
DCV/SOF	£67,455	15.719	£39,560	1.439	£27,492
GT1a TE C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£55,175	7.850	-	-	-
SMV/PR	£61,679	8.912	£6,504	1.062	£6,124
SOF/PR	£65,426	8.838	£10,252	0.988	£10,377
EBR/GZR	£67,287	9.415	£12,113	1.565	£7,739
LDV/SOF	£69,467	9.436	£14,292	1.587	£9,006
2D/3D	£94,679	9.457	£39,504	1.607	£24,580
GT1a TE NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£28,797	13.215	-	-	-
BSC	£28,835	11.907	£38	-1.309	Dominated
SMV/PR	£36,951	14.335	£8,154	1.120	£7,281
2D/3D	£42,250	14.757	£13,453	1.542	£8,726
EBR/GZR	£44,540	14.646	£15,743	1.431	£11,003
LDV/SOF	£46,082	14.757	£17,286	1.542	£11,210
SOF/PR	£47,113	14.327	£18,316	1.111	£16,481
DCV/SOF	£66,910	14.721	£38,114	1.505	£25,320

Abbreviations.ICER:incremental cost-effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve; QALYs:quality-adjusted life years

Table 5.43: ERG pairwise base-case analyses for GT1b (TN/TE; C/NC), all comparisons against PR

GT1b TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,884	8.390	-	-	-
SOF/PR	£62,628	9.754	£7,743	1.364	£5,675
2D/3D	£64,947	9.975	£10,062	1.585	£6,348
SMV/PR	£65,571	9.072	£10,687	0.682	£15,676
EBR/GZR	£67,714	10.004	£12,829	1.614	£7,949
LDV/SOF	£70,320	9.978	£15,436	1.588	£9,719
GT1b TN NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£28,094	14.254	-	-	-
BSC	£30,513	12.474	£2,418	-1.780	Dominated
LDV/SOF	£34,398	15.637	£6,304	1.383	£4,558
SMV/PR	£39,097	15.107	£11,003	0.853	£12,897
2D/3D	£42,800	15.745	£14,706	1.491	£9,862
EBR/GZR	£44,505	15.713	£16,411	1.459	£11,247
SOF/PR	£44,704	15.679	£16,610	1.426	£11,650
DCV/SOF	£67,561	15.705	£39,467	1.451	£27,198
GT1b TE C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,008	7.974	£0	0.000	
SMV/PR	£59,760	9.116	£5,751	1.142	£5,035
2D/3D	£62,754	9.576	£8,746	1.602	£5,460
EBR/GZR	£65,304	9.626	£11,296	1.652	£6,837
SOF/PR	£66,777	8.694	£12,769	0.720	£17,737
LDV/SOF	£67,689	9.626	£13,681	1.652	£8,282
GT1b TE NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£29,315	13.153	-	-	-
BSC	£28,835	11.907	-£480	-1.246	£385 (SW)
SMV/PR	£37,127	14.314	£7,813	1.161	£6,730
2D/3D	£41,325	14.858	£12,010	1.705	£7,044
EBR/GZR	£42,993	14.832	£13,678	1.680	£8,144
LDV/SOF	£45,458	14.832	£16,144	1.680	£9,612
SOF/PR	£46,461	14.405	£17,146	1.252	£13,692
DCV/SOF	£66,048	14.824	£36,734	1.672	£21,976

Abbreviations.ICER:incremental cost-effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

Table 5.44: ERG pairwise base-case analyses for GT4 (TN/TE; C/NC), all comparisons against PR

GT4 TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,599	8.423	-	-	-
SOF/PR	£63,401	9.665	£8,802	1.242	£7,086
SMV/PR	£65,380	9.094	£10,781	0.671	£16,071
EBR/GZR	£68,555	9.907	£13,956	1.484	£9,406
LDV/SOF	£70,941	9.907	£16,342	1.484	£11,014
DCV/PR	£84,350	9.943	£29,750	1.520	£19,567
2D/3D	£93,333	9.925	£38,734	1.502	£25,789
GT4 TN NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£27,895	14.280	£0	0.000	
BSC	£30,513	12.474	£2,617	-1.806	Dominated
SMV/PR	£38,763	15.150	£10,868	0.871	£12,483
2D/3D	£40,338	15.727	£12,443	1.447	£8,599
EBR/GZR	£44,892	15.663	£16,997	1.383	£12,287
DCV/PR	£60,712	15.705	£32,817	1.426	£23,016
GT4 TE C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,551	7.916	-	-	-
SMV/PR	£61,311	8.951	£6,760	1.035	£6,531
SOF/PR	£65,426	8.838	£10,875	0.922	£11,801
EBR/GZR	£67,287	9.415	£12,736	1.499	£8,498
LDV/SOF	£69,467	9.436	£14,916	1.520	£9,810
DCV/PR	£82,894	9.472	£28,343	1.556	£18,220
2D/3D	£91,857	9.461	£37,306	1.545	£24,153
GT4 TE NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£28,797	13.215	-	-	-
BSC	£28,835	11.907	£38	-1.309	Dominated
SMV/PR	£36,951	14.335	£8,154	1.120	£7,281
2D/3D	£39,555	14.757	£10,759	1.542	£6,977
EBR/GZR	£44,540	14.646	£15,743	1.431	£11,003
LDV/SOF	£46,082	14.757	£17,286	1.542	£11,210
DCV/PR	£60,166	14.714	£31,369	1.499	£20,923
DCV/SOF	£66,910	14.721	£38,114	1.505	£25,320

Abbreviations.ICER:incremental cost-effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

Table 5.45: ERG full incremental analyses for GT1a (TN/TE; C/NC)

GT1a TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,599	8.423	-	-	-
SOF/PR	£64,907	9.491	£10,308	1.068	£9,647
SMV/PR	£65,380	9.094	£473	-0.398	Dominated by SOF/PR
EBR/GZR	£68,555	9.907	£3,649	0.415	£8,784
LDV/SOF	£70,941	9.907	£2,385	0.000	Dominated by EBR/GZR
2D/3D	£96,765	9.851	£28,210	-0.056	Dominated by EBR/GZR
GT1a TN NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£27,895	14.280	-	-	-
BSC	£30,513	12.474	£2,617	-1.806	Dominated by PR
LDV/SOF	£34,543	15.618	£6,648	1.338	£4,967
SMV/PR	£38,763	15.150	£4,220	-0.468	Dominated by LDV/SOF
2D/3D	£43,033	15.726	£8,490	0.108	£78,280
EBR/GZR	£44,892	15.663	£1,859	-0.064	Dominated by 2D/3D
SOF/PR	£46,239	15.481	£3,206	-0.246	Dominated by 2D/3D
DCV/SOF	£67,455	15.719	£24,422	-0.008	Dominated by 2D/3D
GT1a TE C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£55,175	7.850	-	-	-
SMV/PR	£61,679	8.912	£6,504	1.062	£6,124
SOF/PR	£65,426	8.838	£3,747	-0.074	Dominated by SOF/PR
EBR/GZR	£67,287	9.415	£5,608	0.503	£11,153
LDV/SOF	£69,467	9.436	£2,179	0.022	£99,998
2D/3D	£94,679	9.457	£25,212	0.020	£1,242,000
GT1a TE NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£28,797	13.215	-	-	-
BSC	£28,835	11.907	£38	-1.309	Dominated by PR
SMV/PR	£36,951	14.335	£8,154	1.120	£7,281
2D/3D	£42,250	14.757	£5,300	0.422	£12,557
EBR/GZR	£44,540	14.646	£2,290	-0.111	Dominated by 2D/3D
LDV/SOF	£46,082	14.757	£3,832	0.000	£28,743,149
SOF/PR	£47,113	14.327	£1,030	-0.431	Dominated by LDV/SOF
DCV/SOF	£66,910	14.721	£20,828	-0.037	Dominated by LDV/SOF

Abbreviations.ICER:incremental cost-effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

Table 5.46: ERG full incremental analyses for GT1b (TN/TE; C/NC)

GT1b TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,884	8.390	-	-	-
SOF/PR	£62,628	9.754	£7,743	1.364	£5,675
2D/3D	£64,947	9.975	£2,319	0.221	£10,509
SMV/PR	£65,571	9.072	£625	-0.903	Dominated by 2D/3D
EBR/GZR	£67,714	10.004	£2,767	0.029	£96,084
LDV/SOF	£70,320	9.978	£2,606	-0.026	Dominated by EBR/GZR
GT1b TN NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£28,094	14.254	-	-	-
BSC	£30,513	12.474	£2,418	-1.780	Dominated by PR
LDV/SOF	£34,398	15.637	£6,304	1.383	£4,558
SMV/PR	£39,097	15.107	£4,699	-0.530	Dominated by LDV/SOF
2D/3D	£42,800	15.745	£8,402	0.108	£77,671
EBR/GZR	£44,505	15.713	£1,705	-0.032	Dominated by 2D/3D
SOF/PR	£44,704	15.679	£1,904	-0.065	Dominated by 2D/3D
DCV/SOF	£67,561	15.705	£24,761	-0.040	Dominated by 2D/3D
GT1b TE C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,008	7.974	-	-	-
SMV/PR	£59,760	9.116	£5,751	1.142	£5,035
2D/3D	£62,754	9.576	£2,994	0.459	£6,517
EBR/GZR	£65,304	9.626	£2,550	0.050	£50,767
SOF/PR	£66,777	8.694	£1,473	-0.932	Dominated by EBR/GZR
LDV/SOF	£67,689	9.626	£2,385	0.000	Dominated by EBR/GZR
GT1b TE NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
BSC	£28,835	11.907	-	-	-
PR	£29,315	13.153	£480	1.246	£385
SMV/PR	£37,127	14.314	£7,813	1.161	£6,730
2D/3D	£41,325	14.858	£4,197	0.544	£7,715
EBR/GZR	£42,993	14.832	£1,668	-0.025	Dominated by 2D/3D
LDV/SOF	£45,458	14.832	£4,134	-0.025	Dominated by 2D/3D
SOF/PR	£46,461	14.405	£5,136	-0.453	Dominated by 2D/3D
DCV/SOF	£66,048	14.824	£24,724	-0.033	Dominated by 2D/3D

Abbreviations.ICER:incremental cost-effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

Table 5.47: ERG full incremental analyses for GT4 (TN/TE; C/NC)

GT4 TN C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,599	8.423	£0	0.000	
SOF/PR	£63,401	9.665	£8,802	1.242	£7,086
SMV/PR	£65,380	9.094	£1,979	-0.571	Dominated by SOF/PR
EBR/GZR	£68,555	9.907	£5,154	0.242	£21,335
LDV/SOF	£70,941	9.907	£2,385	0.000	Dominated by EBR/GZR
DCV/PR	£84,350	9.943	£15,794	0.037	£431,886
2D/3D	£93,333	9.925	£8,984	-0.018	Dominated by DCV/PR
GT4 TN NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£27,895	14.280	£0	0.000	
BSC	£30,513	12.474	£2,617	-1.806	Dominated by PR
SMV/PR	£38,763	15.150	£10,868	0.871	Extendedly dominated
2D/3D	£40,338	15.727	£12,443	1.447	£8,599
EBR/GZR	£44,892	15.663	£4,553	-0.064	Dominated by 2D/3D
DCV/PR	£60,712	15.705	£20,374	-0.021	Dominated by 2D/3D
GT4 TE C Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£54,551	7.916	£0	0.000	
SMV/PR	£61,311	8.951	£6,760	1.035	£6,531
SOF/PR	£65,426	8.838	£4,115	-0.113	Dominated by SMV/PR
EBR/GZR	£67,287	9.415	£5,977	0.464	£12,889
LDV/SOF	£69,467	9.436	£2,179	0.022	£99,998
DCV/PR	£82,894	9.472	£13,427	0.035	£382,876
2D/3D	£91,857	9.461	£8,963	-0.011	Dominated by DCV/PR
GT4 TE NC Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PR	£28,797	13.215	£0	0.000	
BSC	£28,835	11.907	£38	-1.309	Dominated by PR
SMV/PR	£36,951	14.335	£8,154	1.120	Extendedly dominated
2D/3D	£39,555	14.757	£10,758	1.542	£6,977
EBR/GZR	£44,540	14.646	£4,984	-0.111	Dominated by 2D/3D
LDV/SOF	£46,082	14.757	£6,527	0.000	Dominated by 2D/3D
DCV/PR	£60,166	14.714	£20,611	-0.043	Dominated by 2D/3D
DCV/SOF	£66,910	14.721	£27,355	-0.037	Dominated by 2D/3D

Abbreviations.ICER:incremental cost-effectiveness ratio;TE:treatment-experienced; TN:treatment-naïve;QALYs:quality-adjusted life years

As can be seen in the provided tables, compared to the base-case from the company, the ERG base-case results for EBR/GZR are similar for patients with cirrhosis across all groups (GT1a, GT1b and GT4), whereas for the patients without cirrhosis, ICER values (vs. PR) increased about £3,000 per QALY gained.

A more detailed assessment of the impact of each individual change to the company base-case can be found in Chapter 6 of this report.

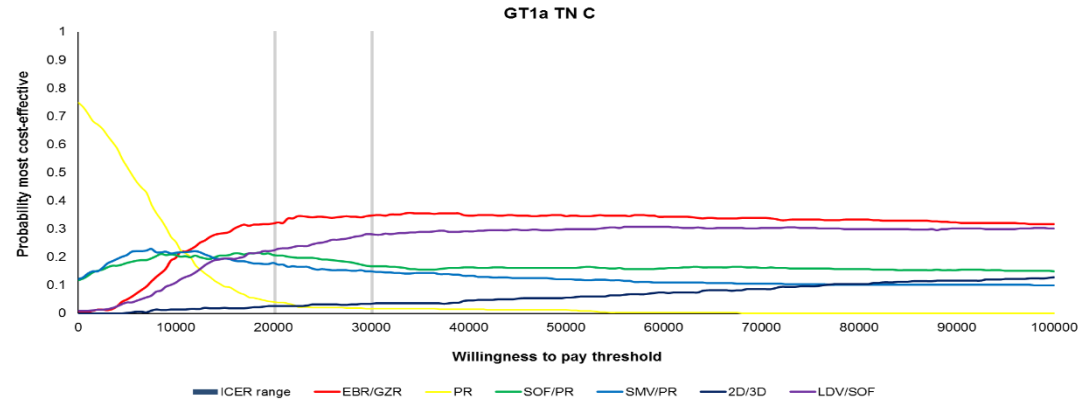
5.3.2 Probabilistic sensitivity analyses

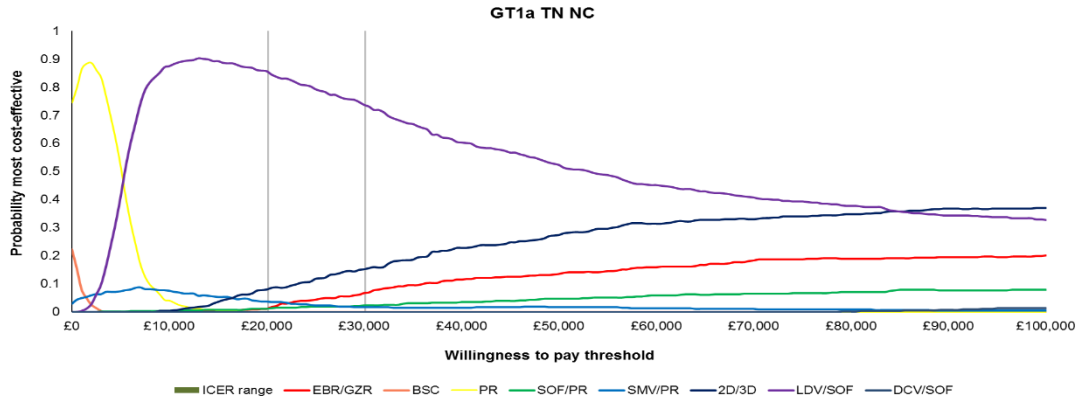
The mean total costs, mean total QALYs and the resultant ICERs for GT1a, GT1b and GT4 populations, stratified based on their treatment experience and presence of cirrhosis from PSA were similar to those from deterministic analysis (results not presented). The CEACs are presented in Figure 5.5, Figure 5.6 and Figure 5.7, respectively.

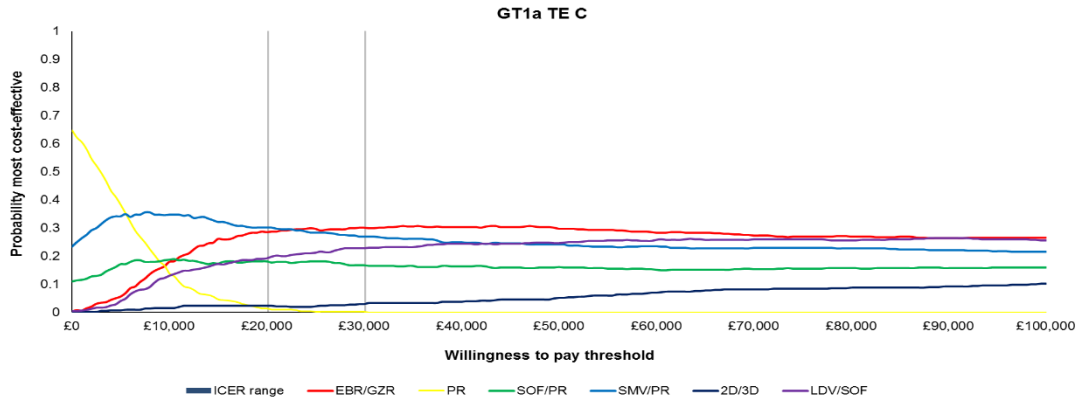
From the CEACs, it could be observed that EBR/GZR becomes the most cost effective intervention in many subgroups. In the GT1a TN C, GT1b TE C and GT4 TN C populations, EBR/GZR becomes the most cost effective treatment option after £15,000 per QALY threshold, whereas in the GT1a TE C, GT1b TN C and GT1b TE NC populations, EBR/GZR becomes the most cost effective around £25,000- £30,000 per QALY thresholds, respectively.

In all other populations, EBR/GZR was not the most cost effective treatment option up to a £100,000 per QALY threshold.

Figure 5.5: Cost effectiveness acceptability curves –GT1a populations







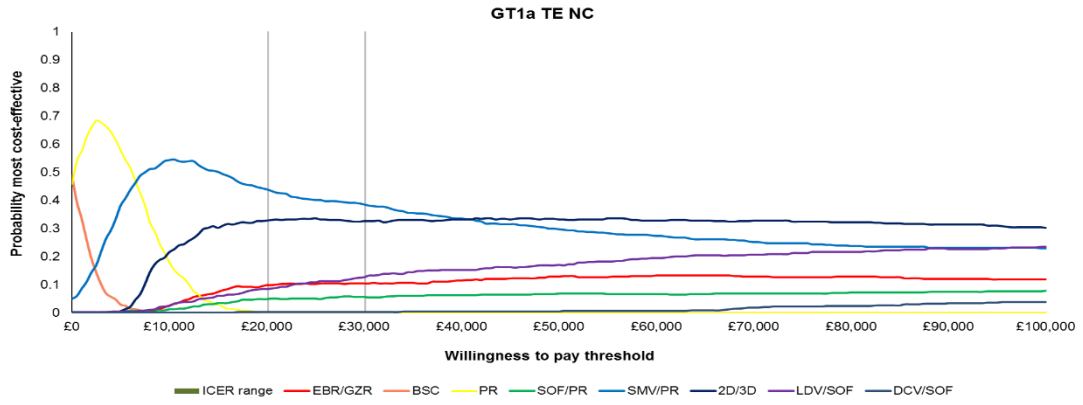
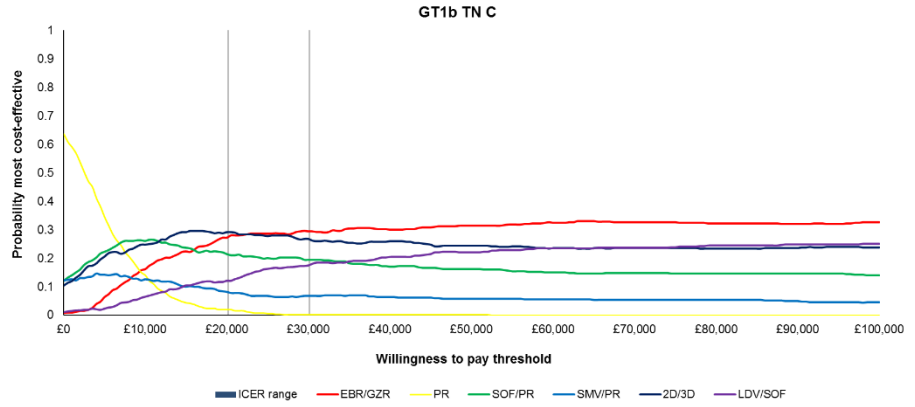
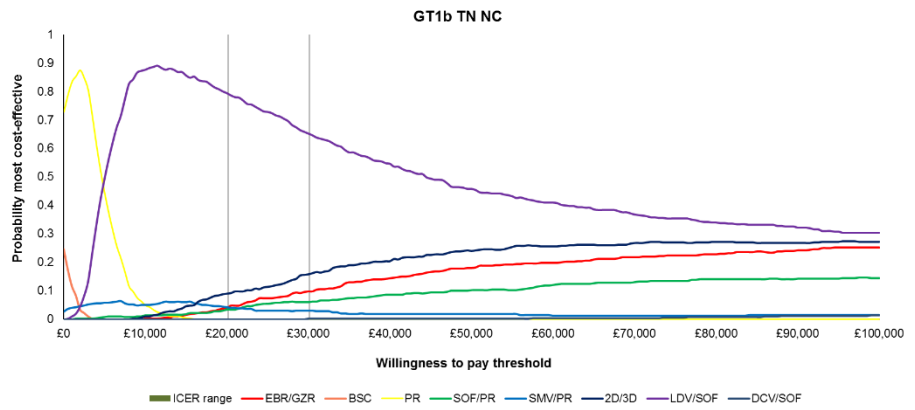
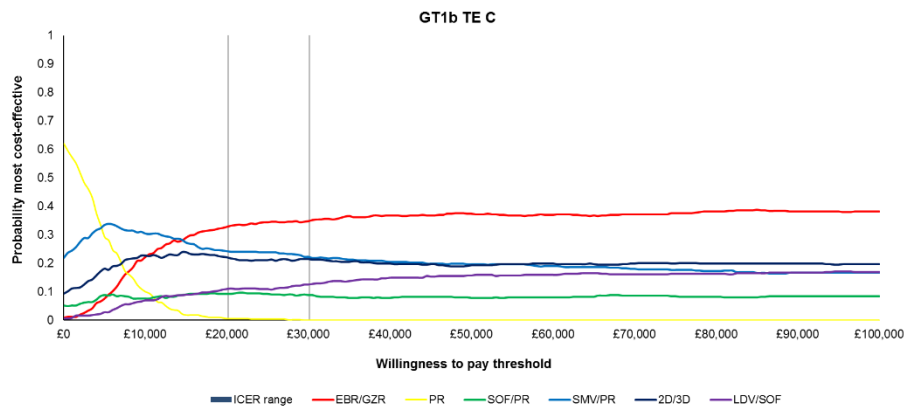


Figure 5.6: Cost effectiveness acceptability curves – GT1b populations







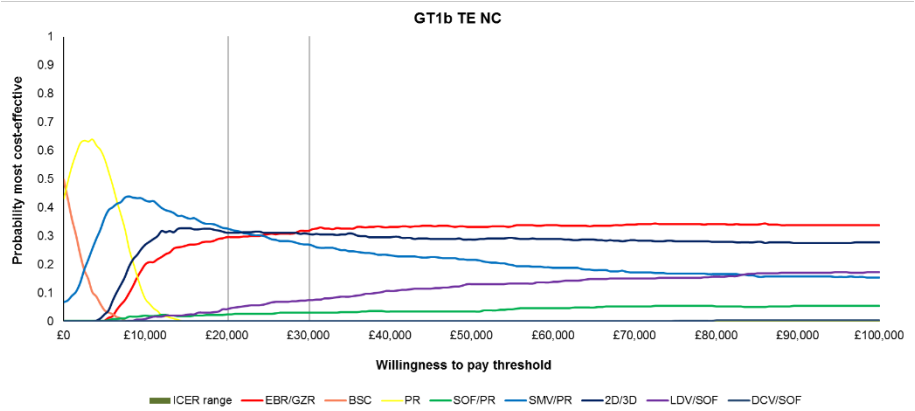
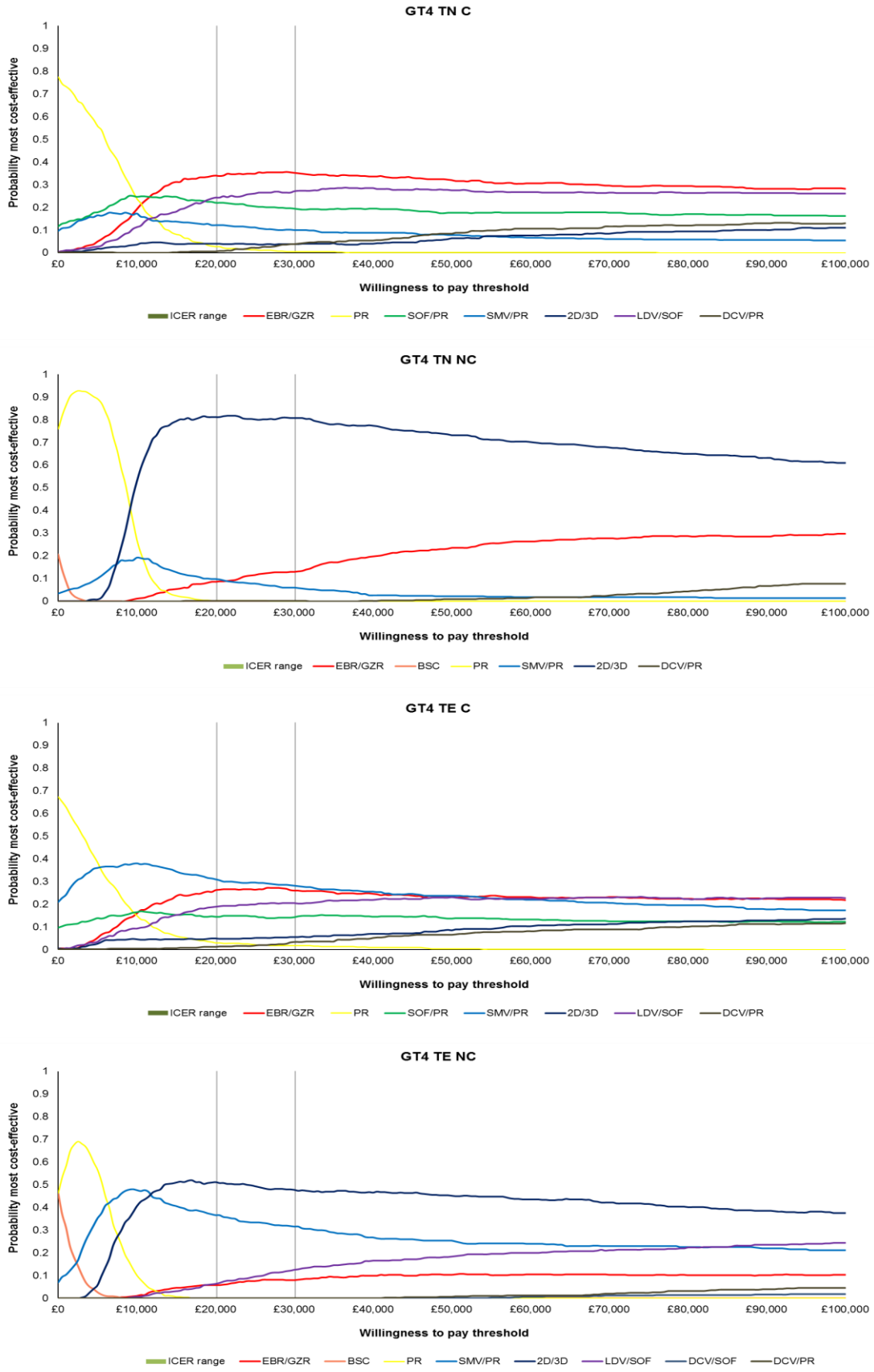


Figure 5.7: Cost effectiveness acceptability curves – GT4 populations



5.3.3 Scenario analyses

A number of scenario analyses were conducted in addition to the base-case analyses, to explore the impact of the assumptions in the model. The scenario analyses are listed below. Most of the scenarios were the same as the scenarios that were described in the CS. Additional scenario analyses were performed to explore the choices made by the ERG. The ERG scenario analyses are described in detail below.

Scenario analysis 1 – use of GT4 specific clinical data instead of applying GT1 data to GT4 patients in the base case:

GT4 population specific NMA results for SVR (Table 5.8), AE probabilities (Table 5.14) and discontinuation rates (Table 5.11) were used for GT4 subgroups for EBR/GZR and comparators when available. (This scenario is conducted only for GT4 populations; hence it will not be seen in the result tables of other GT populations)

Scenario analysis 2 – use of naïve indirect comparison results instead of NMA results in the base case:

The results from naïve indirect comparison for SVR (can be found in Table 5.7), AEs (can be found in Table 5.13) and discontinuation rates (can be found in Table 5.10) were used for EBR/GZR and comparators when available.

Scenario analysis 3 – Using age-dependent transition probabilities across fibrosis health states instead of using age-independent transition probabilities in the base case:

In this scenario, probabilities from Grishchenko et al., 2009[72] were used instead of the transition probabilities from Thein et al., 2008[93] in the base case. In Grishchenko et al., 2009, fibrosis progression rates differing by age were given in Table 5.29. This scenario is only relevant for patients without cirrhosis, as these probabilities are between states F0 and F3. Therefore, this scenario was not listed in cirrhotic patient groups.

Scenario analysis 4 - After re-infection, patient starts from F0 (new):

In the ERG base case scenario, patients return to the health state they were in prior to reaching SVR. This alternative scenario corresponds to the base case analysis in the CS and assumes that after reinfection, patients start from F0. This scenario is only relevant for patients without cirrhosis, as this assumption is related to the transitions between states F0 and F3. Therefore, this scenario was not listed in cirrhotic patient groups.

Scenario analysis 5 - Adverse events:

Apply uniform disutility for AEs to all all-DAA treatments: As described in Section 5.2, the ERG questioned the methodology that was applied to calculate utility decrements due to adverse events for EBR/GZR. In the base case analysis, the utility decrement of EBR/GZR was 0.000. In this scenario analysis, the adverse events treatments disutilities for all all-DAA regimens were set equal to 0.035 (equal to DCV/SOF).

Scenario analysis 6 - Using SVR related utility increments from Wright et al., 2006 (0.05)[67]:

In the ERG base case, the SVR related utility increment estimate (0.03) derived from the European patients from the EBR/GZR trial were used. In this scenario, the estimate from Wright et al., 2006 (0.05)[67] is used similar to the company base-case.

Scenario analysis 7 - Incorporating age based utility decrements: In the ERG base-case, age-based utility decrements were not incorporated. In this scenario, age-based utility decrements are included similar to the CS base case.

The results of the scenario analyses are presented in Tables 5.48 to 5.59 below for GT1a, GT1b and GT4 patient populations, stratified according to TN/TE and C/NC subgroups, respectively.

Similar to the analyses conducted by the company, using GT4 specific data (scenario 1) or using naïve indirect NMA results (scenario 2) have substantial effects on the ICER results. However, there is no unidirectional trend for the ICER changes in these scenarios in between populations and treatments. Therefore, besides acknowledging the presence of the important effects, it is not possible to make any judgements on the direction of the effect of the scenarios 1 and 2 (choice of treatment input effectiveness data) on the ICER values.

Note that scenario 1 was only relevant for GT4 populations, therefore it is not listed in the tables presenting results from GT1a and GT1b populations. Furthermore, if there is an asterisk sign (*) next to the reported ICER value, it means that the corresponding intervention's ICER lies in the southwest quadrant, hence the intervention results in less total costs and less total QALYs.

For all non-cirrhotic patient populations, using the age-specific probabilities specified in scenario 3 had a substantial impact on the ICER values (vs PR) of all the interventions. For all subgroups and interventions, ICERs had increased more than 200% compared to the base-case ICER.

In scenario 4, full reversal of the fibrosis after the SVR has a significant impact on the ICER of the interventions in the non-cirrhotic patient populations. ICER values decreased by £3,000 per QALY gained in general.

From these results, it can be seen that scenario 5 (applying uniform AE related disutilities among all-DAA treatments) had almost no effect on all-DAA treatments' incremental results, and no effect at all for other treatments.

Using the SVR utility increment of (0.05) in scenario 6 had limited impact on incremental QALYS, and in this scenario (scenario 6), ICER of the interventions have decreased around £1,000 per QALY gained in general.

Similarly, incorporating age based decrements in scenario 7 had limited impact on incremental QALYS, and in this scenario (scenario 7), ICER of the interventions have increased around £1,000 per QALY gained in general.

Table 5.48: Incremental costs, QALYs and ICERs for each comparator - GT1a TN C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£10,781	0.671	£16,071	£10,308	1.068	£9,647	£16,342	1.484	£11,014
Scenario 2	£12,234	0.608	£20,131	£16,376	1.069	£15,312	£15,926	1.524	£10,448
Scenario 5	£10,781	0.671	£16,071	£10,308	1.068	£9,647	£16,342	1.476	£11,074
Scenario 6	£10,781	0.751	£14,363	£10,308	1.198	£8,601	£16,342	1.654	£9,878
Scenario 7	£10,781	0.634	£16,992	£10,308	0.974	£10,584	£16,342	1.347	£12,128
	EBR/GZR vs. PR			2D/3D vs. PR					
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER			
Base case	£13,956	1.484	£9,406	£42,166	1.428	£29,526			
Scenario 2	£13,639	1.499	£9,097	£47,800	1.476	£32,388			
Scenario 5	£13,956	1.476	£9,457	£42,166	1.414	£29,827			
Scenario 6	£13,956	1.654	£8,436	£42,166	1.587	£26,574			
Scenario 7	£13,956	1.348	£10,357	£42,166	1.308	£32,228			

Table 5.49: Incremental costs, QALYs and ICERs for each comparator -GT1a TN NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£2,617	-1.806	Dominated	£10,868	0.871	£12,483	£18,344	1.201	£15,271
Scenario 2	£2,297	-1.772	Dominated	£10,085	0.994	£10,149	£17,275	1.353	£12,772
Scenario 3	-£3,011	-0.778	£3,871*	£13,696	0.353	£38,819	£22,331	0.471	£47,422
Scenario 4	£3,932	-2.009	Dominated	£10,113	0.987	£10,245	£17,275	1.366	£12,645
Scenario 5	£2,617	-1.806	Dominated	£10,868	0.871	£12,483	£18,344	1.201	£15,271
Scenario 6	£2,617	-1.986	Dominated	£10,868	0.974	£11,160	£18,344	1.347	£13,615
Scenario 7	£2,617	-1.694	Dominated	£10,868	0.862	£12,602	£18,344	1.164	£15,757
	LDV/SOF vs. PR			EBR/GZR vs. PR			DCV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£6,648	1.338	£4,967	£16,997	1.383	£12,287	£39,560	1.439	£27,492
Scenario 2	£6,570	1.342	£4,897	£16,676	1.417	£11,770	£39,280	1.473	£26,675
Scenario 3	£11,006	0.540	£20,374	£21,460	0.566	£37,920	£44,228	0.584	£75,691
Scenario 4	£5,479	1.519	£3,607	£15,809	1.567	£10,091	£38,321	1.630	£23,508
Scenario 5	£6,648	1.333	£4,987	£16,997	1.375	£12,359	£39,560	1.439	£27,492
Scenario 6	£6,648	1.498	£4,437	£16,997	1.546	£10,996	£39,560	1.608	£24,597
Scenario 7	£6,648	1.292	£5,145	£16,997	1.338	£12,698	£39,560	1.391	£28,444
	2D/3D vs. PR								
	Incr. Costs	Incr. QALYs	ICER						
Base case	£15,138	1.447	£10,462						
Scenario 2	£15,130	1.448	£10,447						
Scenario 3	£19,805	0.592	£33,441						
Scenario 4	£13,899	1.638	£8,485						
Scenario 5	£15,138	1.439	£10,521						
Scenario 6	£15,138	1.616	£9,366						
Scenario 7	£15,138	1.399	£10,823						

Table 5.50: Incremental costs, QALYs and ICERs for each comparator - GT1a TE C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£6,504	1.062	£6,124	£10,252	0.988	£10,377	£14,292	1.587	£9,006
Scenario 2	£7,428	1.059	£7,012	£16,639	0.955	£17,423	£15,167	1.486	£10,205
Scenario 5	£6,504	1.062	£6,124	£10,252	0.988	£10,377	£14,292	1.579	£9,052
Scenario 6	£6,504	1.191	£5,462	£10,252	1.114	£9,204	£14,292	1.776	£8,047
Scenario 7	£6,504	1.016	£6,400	£10,252	0.940	£10,903	£14,292	1.503	£9,512
	EBR/GZR vs. PR			2D/3D vs. PR					
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER			
Base case	£12,113	1.565	£7,739	£39,504	1.607	£24,580			
Scenario 2	£12,868	1.464	£8,789	£45,568	1.606	£28,373			
Scenario 5	£12,113	1.557	£7,779	£39,504	1.593	£24,802			
Scenario 6	£12,113	1.752	£6,914	£39,504	1.792	£22,040			
Scenario 7	£12,113	1.482	£8,172	£39,504	1.528	£25,858			

Table 5.51: Incremental costs, QALYs and ICERs for each comparator - GT1a TE NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£38	-1.309	Dominated	£8,154	1.120	£7,281	£18,316	1.111	£16,481
Scenario 2	-£565	-1.244	£454*	£8,114	1.144	£7,090	£18,390	1.114	£16,505
Scenario 3	-£4,184	-0.589	£7,108*	£12,042	0.456	£26,419	£22,249	0.439	£50,645
Scenario 4	£999	-1.449	Dominated	£7,146	1.267	£5,638	£17,275	1.264	£13,670
Scenario 5	£38	-1.309	Dominated	£8,154	1.120	£7,281	£18,316	1.111	£16,481
Scenario 6	£38	-1.443	Dominated	£8,154	1.261	£6,468	£18,316	1.257	£14,575
Scenario 7	£38	-1.262	Dominated	£8,154	1.112	£7,332	£18,316	1.098	£16,684
	LDV/SOF vs. PR			EBR/GZR vs. PR			DCV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£17,286	1.542	£11,210	£15,743	1.431	£11,003	£38,114	1.505	£25,320
Scenario 2	£16,669	1.607	£10,373	£15,140	1.496	£10,122	£36,479	1.700	£21,464
Scenario 3	£22,564	0.641	£35,227	£20,645	0.594	£34,782	£43,295	0.620	£69,787
Scenario 4	£15,911	1.743	£9,128	£14,462	1.618	£8,937	£36,763	1.703	£21,588
Scenario 5	£17,286	1.534	£11,269	£15,743	1.423	£11,065	£38,114	1.505	£25,320
Scenario 6	£17,286	1.734	£9,969	£15,743	1.610	£9,781	£38,114	1.694	£22,502
Scenario 7	£17,286	1.518	£11,390	£15,743	1.409	£11,169	£38,114	1.482	£25,722
	2D/3D vs. PR								
	Incr. Costs	Incr. QALYs	ICER						
Base case	£13,453	1.542	£8,726						
Scenario 2	£12,672	1.636	£7,745						
Scenario 3	£18,731	0.640	£29,250						
Scenario 4	£12,079	1.743	£6,930						
Scenario 5	£13,453	1.534	£8,771						
Scenario 6	£13,453	1.734	£7,760						
Scenario 7	£13,453	1.518	£8,865						

Table 5.52: Incremental costs, QALYs and ICERs for each comparator - GT1b TN C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£10,687	0.682	£15,676	£7,743	1.364	£5,675	£15,436	1.588	£9,719
Scenario 2	£12,349	0.594	£20,775	£13,996	1.344	£10,413	£16,001	1.516	£10,557
Scenario 5	£10,687	0.682	£15,676	£7,743	1.364	£5,675	£15,436	1.580	£9,768
Scenario 6	£10,687	0.763	£14,013	£7,743	1.527	£5,072	£15,436	1.770	£8,720
Scenario 7	£10,687	0.644	£16,593	£7,743	1.236	£6,264	£15,436	1.440	£10,719
	EBR/GZR vs. PR			2D/3D vs. PR					
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER			
Base case	£12,829	1.614	£7,949	£10,062	1.585	£6,348			
Scenario 2	£12,846	1.591	£8,076	£11,623	1.590	£7,309			
Scenario 5	£12,829	1.606	£7,989	£10,062	1.578	£6,378			
Scenario 6	£12,829	1.799	£7,133	£10,062	1.767	£5,694			
Scenario 7	£12,829	1.463	£8,771	£10,062	1.436	£7,005			

Table 5.53: Incremental costs, QALYs and ICERs for each comparator -GT1b TN NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£2,418	-1.780	Dominated	£11,003	0.853	£12,897	£16,610	1.426	£11,650
Scenario 2	£2,172	-1.756	Dominated	£10,158	0.984	£10,322	£16,525	1.450	£11,400
Scenario 3	-£3,128	-0.767	£4,077*	£13,775	0.346	£39,861	£21,316	0.564	£37,792
Scenario 4	£3,712	-1.980	Dominated	£10,262	0.968	£10,607	£15,361	1.618	£9,491
Scenario 5	£2,418	-1.780	Dominated	£11,003	0.853	£12,897	£16,610	1.426	£11,650
Scenario 6	£2,418	-1.957	Dominated	£11,003	0.954	£11,528	£16,610	1.596	£10,404
Scenario 7	£2,418	-1.669	Dominated	£11,003	0.846	£13,007	£16,610	1.377	£12,063
	LDV/SOF vs. PR			EBR/GZR vs. PR			DCV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£6,304	1.383	£4,558	£16,411	1.459	£11,247	£39,467	1.451	£27,198
Scenario 2	£5,336	1.501	£3,554	£16,165	1.483	£10,901	£38,830	1.531	£25,366
Scenario 3	£10,805	0.559	£19,339	£21,117	0.597	£35,350	£44,173	0.589	£74,953
Scenario 4	£5,099	1.569	£3,250	£15,162	1.652	£9,179	£38,218	1.644	£23,250
Scenario 5	£6,304	1.378	£4,576	£16,411	1.451	£11,309	£39,467	1.451	£27,198
Scenario 6	£6,304	1.548	£4,073	£16,411	1.630	£10,069	£39,467	1.622	£24,335
Scenario 7	£6,304	1.334	£4,724	£16,411	1.410	£11,636	£39,467	1.402	£28,144
	2D/3D vs. PR								
	Incr. Costs	Incr. QALYs	ICER						
Base case	£14,706	1.491	£9,862						
Scenario 2	£14,284	1.539	£9,282						
Scenario 3	£19,515	0.611	£31,954						
Scenario 4	£13,432	1.688	£7,958						
Scenario 5	£14,706	1.483	£9,915						
Scenario 6	£14,706	1.665	£8,830						
Scenario 7	£14,706	1.441	£10,207						

Table 5.54: Incremental costs, QALYs and ICERs for each comparator - GT1b TE C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£5,751	1.142	£5,035	£12,769	0.720	£17,737	£13,681	1.652	£8,282
Scenario 2	£7,745	1.026	£7,552	£21,355	0.453	£47,143	£15,483	1.453	£10,659
Scenario 5	£5,751	1.142	£5,035	£12,769	0.720	£17,737	£13,681	1.644	£8,322
Scenario 6	£5,751	1.280	£4,493	£12,769	0.815	£15,661	£13,681	1.849	£7,401
Scenario 7	£5,751	1.091	£5,271	£12,769	0.690	£18,500	£13,681	1.563	£8,751
	EBR/GZR vs. PR			2D/3D vs. PR					
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER			
Base case	£11,296	1.652	£6,837	£8,746	1.602	£5,460			
Scenario 2	£11,320	1.629	£6,949	£10,536	1.582	£6,660			
Scenario 5	£11,296	1.644	£6,871	£8,746	1.594	£5,485			
Scenario 6	£11,296	1.849	£6,110	£8,746	1.793	£4,877			
Scenario 7	£11,296	1.563	£7,225	£8,746	1.516	£5,769			

Table 5.55: Incremental costs, QALYs and ICERs for each comparator - GT1b TE NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	-£480	-1.246	£385*	£7,813	1.161	£6,730	£17,146	1.252	£13,692
Scenario 2	-£392	-1.264	£310*	£7,966	1.162	£6,854	£17,395	1.234	£14,095
Scenario 3	-£4,491	-0.562	£7,987*	£11,840	0.473	£25,022	£21,557	0.499	£43,212
Scenario 4	£428	-1.379	Dominated	£6,770	1.313	£5,154	£15,987	1.422	£11,243
Scenario 5	-£480	-1.246	£385*	£7,813	1.161	£6,730	£17,146	1.252	£13,692
Scenario 6	-£480	-1.373	£350	£7,813	1.306	£5,980	£17,146	1.414	£12,125
Scenario 7	-£480	-1.201	£400*	£7,813	1.152	£6,780	£17,146	1.235	£13,884
	LDV/SOF vs. PR			EBR/GZR vs. PR			DCV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£16,144	1.680	£9,612	£13,678	1.680	£8,144	£36,734	1.672	£21,976
Scenario 2	£16,452	1.633	£10,074	£13,766	1.661	£8,286	£36,651	1.679	£21,832
Scenario 3	£21,887	0.699	£31,328	£19,422	0.699	£27,799	£42,477	0.691	£61,506
Scenario 4	£14,654	1.898	£7,722	£12,188	1.898	£6,423	£35,244	1.890	£18,651
Scenario 5	£16,144	1.672	£9,658	£13,678	1.672	£8,183	£36,734	1.672	£21,976
Scenario 6	£16,144	1.888	£8,552	£13,678	1.888	£7,246	£36,734	1.880	£19,544
Scenario 7	£16,144	1.652	£9,775	£13,678	1.652	£8,282	£36,734	1.644	£22,350
	2D/3D vs. PR								
	Incr. Costs	Incr. QALYs	ICER						
Base case	£12,010	1.705	£7,044						
Scenario 2	£12,105	1.687	£7,177						
Scenario 3	£17,839	0.709	£25,147						
Scenario 4	£10,499	1.926	£5,451						
Scenario 5	£12,010	1.697	£7,077						
Scenario 6	£12,010	1.916	£6,268						
Scenario 7	£12,010	1.676	£7,164						

Table 5.56: Incremental costs, QALYs and ICERs for each comparator – GT4 TN C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£10,781	0.671	£16,071	£8,802	1.242	£7,086	£16,342	1.484	£11,014
Scenario 1	£6,801	1.604	£4,240	£2,958	1.777	£1,664	£14,724	2.071	£7,109
Scenario 2	£12,234	0.608	£20,131	£14,719	1.261	£11,676	£15,926	1.524	£10,448
Scenario 5	£10,781	0.671	£16,071	£8,802	1.242	£7,086	£16,342	1.476	£11,074
Scenario 6	£10,781	0.751	£14,363	£8,802	1.391	£6,328	£16,342	1.654	£9,878
Scenario 7	£10,781	0.634	£16,992	£8,802	1.128	£7,804	£16,342	1.347	£12,128
	EBR/GZR vs. PR			DCV/PR vs. PR			2D/3D vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£13,956	1.484	£9,406	£29,750	1.520	£19,567	£38,734	1.502	£25,789
Scenario 1	£11,547	2.070	£5,577	£13,685	1.530	£8,943	£26,582	2.048	£12,982
Scenario 2	£13,639	1.499	£9,097	£29,219	1.562	£18,710	£41,745	1.548	£26,972
Scenario 5	£13,956	1.476	£9,457	£29,750	1.520	£19,567	£38,734	1.487	£26,049
Scenario 6	£13,956	1.654	£8,436	£29,750	1.694	£17,559	£38,734	1.668	£23,220
Scenario 7	£13,956	1.348	£10,357	£29,750	1.386	£21,471	£38,734	1.375	£28,176

Table 5.57: Incremental costs, QALYs and ICERs for each comparator -GT4 TN NC

	BSC vs. PR			SMV/PR vs. PR			EBR/GZR vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£2,617	-1.806	Dominated	£10,868	0.871	£12,483	£16,997	1.383	£12,287
Scenario 1	£1,015	-1.448	Dominated	£7,397	1.498	£4,938	£15,276	1.750	£8,731
Scenario 2	£2,297	-1.772	Dominated	£10,085	0.994	£10,149	£16,676	1.417	£11,770
Scenario 3	-£2,029	-0.951	£2,133*	£13,202	0.440	£29,995	£20,680	0.704	£29,385
Scenario 4	£3,932	-2.009	Dominated	£10,113	0.987	£10,245	£15,809	1.567	£10,091
Scenario 5	£2,617	-1.806	Dominated	£10,868	0.871	£12,483	£16,997	1.375	£12,359
Scenario 6	£2,617	-1.986	Dominated	£10,868	0.974	£11,160	£16,997	1.546	£10,996
Scenario 7	£2,617	-1.694	Dominated	£10,868	0.862	£12,602	£16,997	1.338	£12,698

	DCV/PR vs. PR			2D/3D vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£32,817	1.426	£23,016	£12,443	1.447	£8,599
Scenario 1	£33,297	0.921	£36,170	£11,140	1.750	£6,368
Scenario 2	£32,277	1.492	£21,634	£12,129	1.481	£8,192
Scenario 3	£36,683	0.713	£51,441	£16,295	0.737	£22,124
Scenario 4	£31,598	1.614	£19,579	£11,204	1.638	£6,839
Scenario 5	£32,817	1.426	£23,016	£12,443	1.439	£8,647
Scenario 6	£32,817	1.592	£20,608	£12,443	1.616	£7,698
Scenario 7	£32,817	1.387	£23,654	£12,443	1.399	£8,895

Table 5.58: Incremental costs, QALYs and ICERs for each comparator – GT4 TE C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£6,760	1.035	£6,531	£10,875	0.922	£11,801	£14,916	1.520	£9,810
Scenario 1	£16,382	0.451	£36,326	£9,304	0.963	£9,659	£16,435	1.732	£9,489
Scenario 2	£7,428	1.059	£7,012	£16,639	0.955	£17,423	£15,167	1.486	£10,205
Scenario 5	£6,760	1.035	£6,531	£10,875	0.922	£11,801	£14,916	1.512	£9,862
Scenario 6	£6,760	1.160	£5,825	£10,875	1.040	£10,458	£14,916	1.702	£8,762
Scenario 7	£6,760	0.991	£6,821	£10,875	0.878	£12,381	£14,916	1.441	£10,353
	EBR/GZR vs. PR			DCV/PR vs. PR			2D/3D vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£12,736	1.499	£8,498	£28,343	1.556	£18,220	£37,306	1.545	£24,153
Scenario 1	£20,720	0.937	£22,125	£12,006	1.593	£7,537	£28,299	1.714	£16,512
Scenario 2	£12,868	1.464	£8,789	£27,352	1.642	£16,659	£40,135	1.606	£24,986
Scenario 5	£12,736	1.491	£8,544	£28,343	1.556	£18,220	£37,306	1.530	£24,390
Scenario 6	£12,736	1.678	£7,590	£28,343	1.740	£16,285	£37,306	1.722	£21,663
Scenario 7	£12,736	1.420	£8,967	£28,343	1.477	£19,189	£37,306	1.470	£25,380

Table 5.59: Incremental costs, QALYs and ICERs for each comparator – GT4 TE NC

	BSC vs. PR			SMV/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£38	-1.309	Dominated	£8,154	1.120	£7,281	£17,286	1.542	£11,210
Scenario 1	£623	-1.237	Dominated	£11,800	0.848	£13,918	£16,930	1.714	£9,878
Scenario 2	-£565	-1.244	£454	£8,114	1.144	£7,090	£16,669	1.607	£10,373
Scenario 3	-£3,455	-0.710	£4,867*	£11,370	0.568	£20,031	£21,652	0.792	£27,326
Scenario 4	£999	-1.449	Dominated	£7,146	1.267	£5,638	£15,911	1.743	£9,128
Scenario 5	£38	-1.309	Dominated	£8,154	1.120	£7,281	£17,286	1.534	£11,269
Scenario 6	£38	-1.443	Dominated	£8,154	1.261	£6,468	£17,286	1.734	£9,969
Scenario 7	£38	-1.262	Dominated	£8,154	1.112	£7,332	£17,286	1.518	£11,390
	EBR/GZR vs. PR			DCV/PR vs. PR			DCV/SOF vs. PR		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£15,743	1.431	£11,003	£31,369	1.499	£20,923	£38,114	1.505	£25,320
Scenario 1	£14,514	1.714	£8,467	£32,345	0.970	£33,345	£37,203	1.706	£21,808
Scenario 2	£15,140	1.496	£10,122	£29,736	1.692	£17,569	£36,479	1.700	£21,464
Scenario 3	£19,798	0.735	£26,952	£35,669	0.761	£46,855	£42,400	0.769	£55,105
Scenario 4	£14,462	1.618	£8,937	£30,037	1.694	£17,730	£36,763	1.703	£21,588
Scenario 5	£15,743	1.423	£11,065	£31,369	1.499	£20,923	£38,114	1.505	£25,320
Scenario 6	£15,743	1.610	£9,781	£31,369	1.685	£18,614	£38,114	1.694	£22,502
Scenario 7	£15,743	1.409	£11,169	£31,369	1.481	£21,177	£38,114	1.482	£25,722
	2D/3D vs. PR								
	Incr. Costs	Incr. QALYs	ICER						
Base case	£10,759	1.542	£6,977						
Scenario 1	£10,378	1.714	£6,055						
Scenario 2	£9,920	1.636	£6,062						
Scenario 3	£15,125	0.792	£19,088						
Scenario 4	£9,384	1.743	£5,384						
Scenario 5	£10,759	1.534	£7,014						
Scenario 6	£10,759	1.734	£6,205						
Scenario 7	£10,759	1.518	£7,089						

5.4 Conclusions of the cost effectiveness section

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent and is in line with the decision problem specified in the scope.

The ERG assessment indicated that the model was presented and reported appropriately. The cost effectiveness analysis resembled previous STAs for HCV treatments in many aspects. The company developed a de novo cost effectiveness model to assess the cost effectiveness of EBR/GZR compared to various comparators: PR, BSC, SOF/PR, SMV/PR, 2D or 3D based regimens, LDV/SOF and DCV based regimens (DCV/PR or DCV/SOF). BOC/PR and TVR/PR and SMV/SOF treatments were not considered as a comparator, as they were not part of the current clinical practice according to the company.

The population in the cost effectiveness analysis was divided into 12 subpopulations. Patients were divided into three genotypes (GT; GT1a, GT1b and GT4); treatment experience (treatment naïve and treatment experienced); and divided according to cirrhosis status (cirrhotic and non-cirrhotic patients). Some of the populations mentioned in the final scope (e.g. HIV co-infected patients or interferon ineligible) were excluded from the cost effectiveness analysis. 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. patient may be intolerant or inadequate responder to the previous therapy, or a patient may have already received a DAA treatment, or maybe DAA naïve, EBR/GZR may have different effectiveness in each of these groups).

The company developed a Markov model consisting of 13 health states. Non-cirrhotic patients in the model start in states F0-F3, and cirrhotic patients start in state F4 (compensated cirrhosis). Patients then may either remain in their current health state or move to a more severe health state of liver disease. After reaching compensated cirrhosis, patients are assumed to have a risk of developing decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), which would possibly lead to liver transplantation. In the model, after a successful treatment, it is assumed that patient achieve SVR, and patients who do not achieve SVR are at the same risk of disease progression as untreated patients.

The current model structure did not allow for sequential treatments. However, 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.

In the model it was assumed that non-cirrhotic patients recover from their fibrosis levels completely over time, and therefore, after reinfection, they start disease without fibrosis (F0). The ERG finds this assumption not plausible, since there is no clinical consensus on this and no evidence was provided by the company.

Another drawback of the modelling approach was its static structure; a dynamic modelling approach might have reflected the decrease in reinfection rates in the population level.

Treatment effectiveness was modelled in terms of SVR rates. Other treatment specific model input parameters were treatment duration, discontinuation and treatment-related adverse event rates. All

other clinical inputs were not treatment related. NMAs were performed in order to identify the appropriate SVR, discontinuation and AE rates for EBR/GZR and its comparators. Because only limited data was available for GT4 patients, data for GT1a patients was used for these patients. The company also provided analysis based on indirect naïve comparison data.

The ERG has concerns on the plausibility of both approaches, which are not in line with the evidence synthesis best practices and susceptible to bias.

Other disease-progression related transition probabilities were not dependent on the treatment, however some sources were older than 10 years, and may be outdated.

Utility values were derived from a study published by Wright et al., 2006.[67] In addition to health state utilities, age-dependent utility decrements were included, based on utility values of the general UK population. Furthermore, treatment-specific utility decrements were included to assess adverse events. Utility increments for SVR were based on the study by Wright et al., 2006.[67]

In the EBR/GZR RCTs, HRQoL was measured with the EQ-5D-5L. These were valued using a 5L-3L crosswalk and then the UK 3L value set. Despite a request from the ERG, the company declined to value the EQ-5D-5L descriptive with the UK 5L value set, thus introducing bias in the utility values. Despite this, the ERG finds it unfortunate that the utilities from the RCTs were not used by the company in their cost effectiveness analysis. The baseline utilities of the HCV patients in the trials were higher than the utilities in the literature. On the other hand, measured utility increment after SVR in the trials were smaller than the reported values in the literature.

The ERG has methodological concerns on how the disutilities due to AEs and how the age-based utility decrements were applied in the model.

List prices for EBR/GZR and comparator treatments were used in the cost effectiveness analysis. Besides drug acquisition costs, costs for monitoring and follow-up and costs related to adverse events were included in the cost effectiveness analysis, all based on previous studies.

The ERG was unsure about the completeness of the health state costs, and thinks that the cost effectiveness analysis based on list prices may not reflect the actual value for money of the HCV treatments.

In all subgroups, PR was the treatment that resulted in minimum costs. For GT1a and GT4 populations, ICER (compared to PR) values for EBR/GZR were around £9,000 per QALY gained for TN and around £8,000 per QALY gained for TE patients. For GT1b, in the TN populations, ICER (compared to PR) values were around £8,000 per QALY gained, whereas for the TE populations, ICER values were about £6,000 per QALY gained. From the full incremental analysis (presented in an appendix to CS), EBR/GZR appeared to be cost effective only in GT1a TN C, GT1a TE C and GT4 TE C populations. In all other populations, EBR/GZR was either dominated by the other cost effective interventions, or the ICER values compared to the previous cost effective interventions were above the £20,000 per QALY gained threshold.

Next to the base case analyses, probabilistic sensitivity analyses and scenario analyses were conducted. Deterministic sensitivity analyses showed that the following input parameters had the

largest influence on the ICER: utility value used for the F4 health state, starting age in the model, drug costs of EBR/GZR and of comparators, SVR of EBR/GZR, and RR of the SVR of the comparators.

PSA results confirm the deterministic results and the mean of the PSA results are in line with the deterministic results. In the GT1a TN C and GT4 TN C populations, EBR/GZR becomes the most cost effective treatment option after £15,000 per QALY willingness to pay threshold, whereas in the GT1a TE C, and GT4 TE C populations, it becomes the most cost effective after £20,000 per QALY. For GT1b TN C, GT1b TE C and GT1b TE NC populations, EBR/GZR becomes the most cost effective after £40,000, £15,000 and £20,000 per QALY thresholds, respectively. In all other populations, EBR/GZR was never the most cost effective treatment option no matter how high the threshold is set.

Scenario analyses revealed that the treatments do not become cost effective for shorter time horizons compared to PR. For non-cirrhotic patients, using age-dependent disease progression transition probabilities increases the ICER between 100% and 300% in all subgroups for all new all-DAA agents. The choice of NMA or indirect naïve treatment data had a significant impact on incremental results, but the effect is not in one direction and different for each subgroup and different treatment. The same holds for the choice of using or not using the GT4 specific data. The ERG can only conclude that these are important choices, but cannot critique whether one choice is more favourable to the other in terms of the incremental results.

The ERG is concerned over the validation status of the cost effectiveness analysis by the company. No details were given concerning the expert validation by the external health economist as well as by the clinical specialists, and no validation exercises such as cross-validation, validation against external data, validation against internal data had been conducted.

Based on the uncertainties in the CS base-case, the ERG created a new base-case by not assuming full recovery from fibrosis after SVR, and by applying SVR utility increase estimate derived from RCT and not implementing the age-based decrements.

The findings of the ERG base-case analysis are generally in line with those from CS. For GT1a and GT4 populations, ICER (compared to PR) values for EBR/GZR were around £8,000-£9,000 per QALY gained for cirrhosis patients and around £11,000-£12,000 per QALY gained for non-cirrhosis patients. For GT1b, in the TN and NC populations, ICER (compared to PR) was almost £13,000 per QALY gained, whereas for the other GT1b populations, ICER values were around £8,000 per QALY gained.

From the full incremental analysis, EBR/GZR appeared to be cost effective only in GT1a TN C, GT1a TE C and GT4 TE C populations. In GT4 TN C population, EBR/GZR resulted in an ICER around the £20,000 per QALY gained threshold, and in all other populations, EBR/GZR was either dominated by the other cost effective interventions, or the ICER values compared to the other cost effective interventions were above the £20,000 per QALY gained threshold.

Findings from the PSA and scenario analyses were also comparable to the CS base-case. Choice of the evidence synthesis approach and using GT4 specific data for GT4 subgroup had significant impacts on the ICER across all groups.

In general EBR/GZR seems to be cost effective compared to PR in all subgroups. However, when all comparators are considered in the full incremental analysis, it is cost effective only in GT1a TN C, GT1a TE C and GT4 TE C populations both in the analyses from the company and the ERG. However, these results should be interpreted with caution, as they were based on list prices and treatment effectiveness parameters that were based on questionable assumptions/methods.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Tables 6.1 to 6.12 show how each individual change of the ERG base-case impacts the ICER plus the combined effect of all changes simultaneously for all relevant populations.

One of the changes to the company base-case will only impact the non-cirrhotic subpopulations, i.e. the change that re-infected SVR F0-F3 patients do not all go to F0, but instead to their pre-SVR state. Thus, this change has not been included in all the cirrhotic (C) subpopulations.

Furthermore, it should be noted that the other two changes relate to the utility increment due to SVR and utility decrement due to age. Thus, only the QALYs and incremental QALYs will be impacted by these changes, whilst the costs remain the same as in the Company base case.

From the odd numbered tables we can clearly observe that changing the SVR utility increment from 0.05 to 0.03 leads to a reduction in incremental QALYs, but this reduction is then counteracted somewhat by the removal of age-based utility decrements, but not fully.

As a result, for all cirrhotic subpopulations the ICER of an intervention against PR will be slightly higher than in the company base-case, without having any impact on the conclusions.

From the even numbered tables we see that, for all pairwise comparisons except BSC versus PR (here PR is always dominant), sending re-infected SVR F0-F3 patients to their pre-SVR state increases the incremental costs while decreasing the incremental QALYs, leading to an increase in the ICER. When then adding the two utility-related changes, the ICER increase further but again, without having any impact on the conclusions.

Table 6.1: Incremental costs, QALYs and ICERs for each comparator -GT1a TN C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£10,781	0.714	£15,095	£10,308	1.104	£9,338	£16,342	1.518	£10,765
SVR utility increment from clinical trials	£10,781	0.634	£16,992	£10,308	1.027	£10,584	£16,342	1.347	£12,128
+ No age-based utility decrements	£10,781	0.671	£16,071	£10,308	1.068	£9,647	£16,342	1.484	£11,014
ERG revised base case	£10,781	0.671	£16,071	£10,308	1.068	£9,647	£16,342	1.484	£11,014
	EBR/GZR vs. PR			**2D/3D vs. PR**					
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**			
Base case from CS	£13,956	1.518	£9,193	£42,166	1.467	£28,742			
SVR utility increment from clinical trials	£13,956	1.348	£10,357	£42,166	1.308	£32,228			
+ No age-based utility decrements	£13,956	1.484	£9,406	£42,166	1.428	£29,526			
ERG revised base case	£13,956	1.484	£9,406	£42,166	1.428	£29,526			

Table 6.2: Incremental costs, QALYs and ICERs for each comparator -GT1a TN NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£3,932	-2.069	Dominated	£10,113	1.077	£9,388	£17,275	1.469	£11.762
Re-infected patients return to their pre-SVR state	£2,617	-1.874	Dominated	£10,868	0.966	£11,255	£18,344	1.310	£14,000
+ SVR utility increment from clinical trials	£2,617	-1.694	Dominated	£10,868	0.862	£12,602	£18,344	1.164	£15,757
+ No age-based utility decrements	£2,617	-1.806	Dominated	£10,868	0.871	£12,483	£18,344	1.201	£15,271
ERG revised base case	£2,617	-1.806	Dominated	£10,868	0.871	£12,483	£18,344	1.201	£15,271
	LDV/SOF vs. PR			**EBR/GZR vs. PR**			**DCV/SOF vs. PR**		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£5,479	1.625	£3,371	£15,809	1.677	£9,427	£38,321	1.744	£21,976
Re-infected patients return to their pre-SVR state	£6,648	1.452	£4,579	£16,997	1.501	£11,325	£39,560	1.560	£25,356
+ SVR utility increment from clinical trials	£6,648	1.292	£5,145	£16,997	1.338	£12,698	£39,560	1.391	£28,444
+ No age-based utility decrements	£6,648	1.338	£4,967	£16,997	1.383	£12,287	£39,560	1.439	£27,492
ERG revised base case	£6,648	1.338	£4,967	£16,997	1.383	£12,287	£39,560	1.439	£27,492
	2D/3D vs. PR								
	Incr. Costs	**Incr. QALYs**	**ICER**						
Base case from CS	£13,899	1.752	£7,935						
Re-infected patients return to their pre-SVR state	£15,138	1,568	£9,654						
+SVR utility increment from clinical trials	£15,138	1.399	£10,823						
+ No age-based utility decrements	£15,138	1.447	£10,462						
ERG revised base case	£15,138	1.447	£10,462						

Table 6.3: Incremental costs, QALYs and ICERs for each comparator - GT1a TE C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£6,504	1.145	£5,681	£10,252	1.066	£9,616	£14,292	1.692	£8,448
SVR utility increment from clinical trials	£6,504	1.016	£6,400	£10,252	0.940	£10,903	£14,292	1.503	£9,512
+ No age-based utility decrements	£6,504	1.062	£6,124	£10,252	0.988	£10,377	£14,292	1.587	£9,006
ERG revised base case	£6,504	1.062	£6,124	£10,252	0.988	£10,377	£14,292	1.587	£9,006
	EBR/GZR vs. PR			**2D/3D vs. PR**					
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**			
Base case from CS	£12,113	1.669	£7,257	£39,504	1.713	£23,062			
SVR utility increment from clinical trials	£12,113	1.482	£8,172	£39,504	1.528	£25,858			
+ No age-based utility decrements	£12,113	1.565	£7,739	£39,504	1.607	£24,580			
ERG revised base case	£12,113	1.565	£7,739	£39,504	1.607	£24,580			

Table 6.4: Incremental costs, QALYs and ICERs for each comparator - GT1a TE NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£999	-1.535	Dominated	£7,146	1.398	£5,112	£17,275	1.393	£12,403
Re-infected patients return to their pre-SVR state	£38	-1.396	Dominated	£8,154	1.253	£6,508	£18,316	1.243	£14,733
+ SVR utility increment from clinical trials	£38	-1.262	Dominated	£8,154	1.112	£7,332	£18,316	1.098	£16,684
+ No age-based utility decrements	£38	-1.309	Dominated	£8,154	1.120	£7,281	£18,316	1.111	£16,481
ERG revised base case	£38	-1.309	Dominated	£8,154	1.120	£7,281	£18,316	1.111	£16,481
	LDV/SOF vs. PR			**EBR/GZR vs. PR**			**DCV/SOF vs. PR**		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£15,911	1.907	£8,343	£14,462	1.773	£8,159	£36,763	1.864	£19,718
Re-infected patients return to their pre-SVR state	£17,286	1.710	£10,111	£15,743	1.558	£9,912	£38,114	1.670	£22,818
+ SVR utility increment from clinical trials	£17,286	1,518	£11,390	£15,743	1.409	£11,169	£38,114	1.482	£25,722
+ No age-based utility decrements	£17,286	1.542	£11,210	£15,743	1.431	£11,003	£34,114	1.505	£25,320
ERG revised base case	£17,286	1.542	£11,210	£15,743	1.431	£11,003	£34,114	1.505	£25,320
	2D/3D vs. PR								
	Incr. Costs	**Incr. QALYs**	**ICER**						
Base case from CS	£12,079	1.907	£6,334						
Re-infected patients return to their pre-SVR state	£13,453	1.709	£7,870						
+ SVR utility increment from clinical trials	£13,453	1.518	£8,865						
+ No age-based utility decrements	£13,453	1.542	£8,726						
ERG revised base case	£13,453	1.542	£8,726						

Table 6.5: Incremental costs, QALYs and ICERs for each comparator - GT1b TN C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£10,687	0.725	£14,741	£7,743	1.398	£5,538	£15,436	1.622	£9,517
SVR utility increment from clinical trials	£10,687	0.644	£16,593	£7,743	1.236	£6,264	£15,436	1.440	£10,719
+ No age-based utility decrements	£10,687	0.682	£15,676	£7,743	1.364	£5,675	£15,436	1.588	£9,719
ERG revised base case	£10,687	0.682	£15,676	£7,743	1.364	£5,675	£15,436	1.588	£9,719

	EBR/GZR vs. PR			2D/3D vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£12,8289	1.647	£7,787	£10,062	1.618	£6,217
SVR utility increment from clinical trials	£12,829	1.463	£8,771	£10,062	1.436	£7,005
+ No age-based utility decrements	£12,829	1.614	£7,949	£10,062	1.585	£6,348
ERG revised base case	£12,829	1.614	£7,949	£10,062	1.585	£6,348

Table 6.6: Incremental costs, QALYs and ICERs for each comparator -GT1b TN NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£3,712	-2.039	Dominated	£10,262	1.057	£9,710	£15,361	1.733	£8,865
Re-infected patients return to their pre-SVR state	£2,418	-1.846	Dominated	£11,003	0.947	£11,616	£16,610	1.548	£10,732
+ SVR utility increment from clinical trials	£2,418	-1.669	Dominated	£11,003	0.846	£13,007	£16,610	1.377	£12,063
+ No age-based utility decrements	£2,418	-1.780	Dominated	£11,003	0.853	£12,897	£16,610	1.426	£11,650
ERG revised base case	£2,418	-1.780	Dominated	£11,003	0.853	£12,897	£16,610	1.426	£11,650
	LDV/SOF vs. PR			**EBR/GZR vs. PR**			**DCV/SOF vs. PR**		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£5,099	1.678	£3,039	£15,162	1.766	£8,585	£38,218	1.758	£21,739
Re-infected patients return to their pre-SVR state	£6,304	1.499	£4,205	£16,411	1.581	£10,380	£39,467	1.573	£25,090
+ SVR utility increment from clinical trials	£6,304	1.334	£4.724	£16,411	1.410	£11,636	£39,467	1.402	£28,144
+ No age-based utility decrements	£6,304	1.383	£4,558	£16,411	1.459	£11,247	£39,467	1.451	£27,198
ERG revised base case	£6,304	1.383	£4,558	£16,411	1.459	£11,247	£39,467	1.451	£27,198
	2D/3D vs. PR								
	Incr. Costs	**Incr. QALYs**	**ICER**						
Base case from CS	£13,432	1.804	£7,446						
Re-infected patients return to their pre-SVR state	£14,706	1.615	£9,106						
+ SVR utility increment from clinical trials	£14,706	1.441	£10,207						
+ No age-based utility decrements	£14,706	1.491	£9,862						
ERG revised base case	£14,706	1.491	£9,862						

Table 6.7: Incremental costs, QALYs and ICERs for each comparator - GT1b TE C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£5,751	1.229	£4,680	£12,769	0.786	£16,253	£13,681	1.760	£7,773
SVR utility increment from clinical trials	£5,751	1.091	£5,271	£12,769	0.690	£18,500	£13,681	1.563	£8,751
+ No age-based utility decrements	£5,751	1.142	£5,035	£12,769	0.720	£17,737	£13,681	1.652	£8,282
ERG revised base case	£5,751	1.142	£5,035	£12,769	0.720	£17,737	£13,681	1.652	£8,282
	EBR/GZR vs. PR			**2D/3D vs. PR**					
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**			
Base case from CS	£11,296	1.760	£6,418	£8,746	1.708	£5,122			
SVR utility increment from clinical trials	£11,296	1.563	£7,225	£8,746	1.516	£5,769			
+ No age-based utility decrements	£11,296	1.652	£6,837	£8,746	1.602	£5,460			
ERG revised base case	£11,296	1.652	£6,837	£8,746	1.602	£5,460			

Table 6.8: Incremental costs, QALYs and ICERs for each comparator - GT1b TE NC

	BSC vs. PR			SMV/PR vs. PR			SOF/PR vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£428	-1.459	Dominated	£6,770	1.448	£4,767	£15,987	1.564	£10,225
Re-infected patients return to their pre-SVR state	-£480	-1.328	£362	£7,813	1.298	£6,020	£17,146	1.397	£12,275
+ SVR utility increment from clinical trials	-£480	-1.201	£400	£7,813	1.152	£6,780	£17,146	1.235	£13,884
+ No age-based utility decrements	-£480	-1.246	£385	£7,813	1.161	£6,730	£17,146	1.252	£13,692
ERG revised base case	-£480	-1.246	£385	£7,813	1.161	£6,730	£17,146	1.252	£13,692
	LDV/SOF vs. PR			**EBR/GZR vs. PR**			**DCV/SOF vs. PR**		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£14,654	2.074	£7,066	£12,188	2.074	£5,877	£35,244	2.066	£17,060
Re-infected patients return to their pre-SVR state	£16,144	1.860	£8,681	£13,678	1.860	£7,355	£36,734	1.852	£19,839
+ SVR utility increment from clinical trials	£16,144	1.652	£9,775	£13,678	1.652	£8,282	£36,734	1.644	£22,350
+ No age-based utility decrements	£16,144	1.680	£9,612	£13,678	1.680	£8,144	£36,734	1.672	£21,976
ERG revised base case	£16,144	1.680	£9,612	£13,678	1.680	£8,144	£36,734	1.672	£21,976
	2D/3D vs. PR								
	Incr. Costs	**Incr. QALYs**	**ICER**						
Base case from CS	£10,499	2.105	£4,988						
Re-infected patients return to their pre-SVR state	£12,010	1.887	£6,363						
+ SVR utility increment from clinical trials	£12,010	1.676	£7,164						
+ No age-based utility decrements	£12,010	1.705	£7,044						
ERG revised base case	£12,010	1.705	£7,044						

Table 6.9: Incremental costs, QALYs and ICERs for each comparator – GT4 TN C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£10,781	0.714	£15,095	£8,802	1.277	£6,894	£16,342	1.518	£10,765
SVR utility increment from clinical trials	£10,781	0.634	£16,992	£8,802	1.128	£7,804	£16,342	1.347	£12,128
+ No age-based utility decrements	£10,781	0.671	£16,071	£8,802	1.242	£7,086	£16,342	1.484	£11,014
ERG revised base case	£10,781	0.671	£16,071	£8,802	1.242	£7,086	£16,342	1.484	£11,014
	EBR/GZR vs. PR			**DCV/PR vs. PR**			**2D/3D vs. PR**		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£13,956	1.518	£9,193	£29,750	1.560	£19,076	£38,734	1.541	£25,138
SVR utility increment from clinical trials	£13,956	1.348	£10,357	£29,750	1.386	£21,471	£38,734	1.375	£28,176
+ No age-based utility decrements	£13,956	1.484	£9,406	£29,750	1.520	£19,567	£38,734	1.502	£25,789
ERG revised base case	£13,956	1.484	£9,406	£29,750	1.520	£19,567	£38,734	1.502	£25,789

Table 6.10: Incremental costs, QALYs and ICERs for each comparator -GT4 TN NC

	BSC vs. PR			SMV/PR vs. PR			EBR/GZR vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£3,932	-2.069	Dominated	£10,113	1.077	£9,388	£15,809	1.677	£9,427
Re-infected patients return to their pre-SVR state	£2,617	-1.874	Dominated	£10,868	0.966	£11,255	£16,997	1.501	£11,325
+ SVR utility increment from clinical trials	£2,617	-1.694	Dominated	£10,868	0.862	£12,602	£16,997	1.338	£12,698
+ No age-based utility decrements	£2,617	-1.806	Dominated	£10,868	0.871	£12,483	£16,997	1.383	£12,287
ERG revised base case	£2,617	-1.806	Dominated	£10,868	0.871	£12,483	£16,997	1.383	£12,287
	DCV/PR vs. PR			**2D/3D vs. PR**					
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**			
Base case from CS	£31,598	1.735	£18,217	£11,204	1.752	£6,396			
Re-infected patients return to their pre-SVR state	£32,817	1.554	£21,118	£12,443	1.568	£7,934			
+ SVR utility increment from clinical trials	£32,817	1.387	£23,654	£12,443	1.399	£8,895			
+ No age-based utility decrements	£32,817	1.426	£23,016	£12,443	1.447	£8,599			
ERG revised base case	£32,817	1.426	£23,016	£12,443	1.447	£8,599			

Table 6.11: Incremental costs, QALYs and ICERs for each comparator – GT4 TE C

	SMV/PR vs. PR			SOF/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£6,760	1.116	£6,055	£10,875	0.997	£10,911	£14,916	1.622	£9,194
SVR utility increment from clinical trials	£6,760	0.991	£6,821	£10,875	0.878	£12,381	£14,916	1.441	£10,353
+ No age-based utility decrements	£6,760	1.035	£6,531	£10,875	0.922	£11,801	£14,916	1.520	£9,810
ERG revised base case	£6,760	1.035	£6,531	£10,875	0.922	£11,801	£14,916	1.520	£9,810
	EBR/GZR vs. PR			**DCV/PR vs. PR**			**2D/3D vs. PR**		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£12,736	1.600	£7,962	£28,343	1.662	£17,054	£37,306	1.647	£22,645
SVR utility increment from clinical trials	£12,736	1.420	£8,967	£28,343	1.477	£19,189	£37,306	1.470	£25,380
+ No age-based utility decrements	£12,736	1.499	£8,498	£28,343	1.556	£18,220	£37,306	1.556	£24,153
ERG revised base case	£12,736	1.499	£8,498	£28,343	1.556	£18,220	£37,306	1.556	£24,153

Table 6.12: Incremental costs, QALYs and ICERs for each comparator – GT4 TE NC

	BSC vs. PR			SMV/PR vs. PR			LDV/SOF vs. PR		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£999	-1.535	Dominated	£7,146	1.398	£5,112	£15,911	1.907	£8,343
Re-infected patients return to their pre-SVR state	£38	-1.396	Dominated	£8,154	1.253	£6,508	£17,286	1.710	£10,111
+ SVR utility increment from clinical trials	£38	-1.262	Dominated	£8,154	1.112	£7,332	£17,286	1.518	£11,390
+ No age-based utility decrements	£38	-1.309	Dominated	£8,154	1.120	£7,281	£17,286	1.542	£11,210
ERG revised base case	£38	-1.309	Dominated	£8,154	1.120	£7,281	£17,286	1.542	£11,210
	EBR/GZR vs. PR			**DCV/PR vs. PR**			**DCV/SOF vs. PR**		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from CS	£14,462	1.773	£8,159	£30,037	1.859	£16,160	£36,763	1.864	£19,718
Re-infected patients return to their pre-SVR state	£15,743	1.588	£9,912	£31,369	1.667	£18,815	£38,114	1.670	£22,818
+ SVR utility increment from clinical trials	£15,743	1.409	£11,169	£31,369	1.481	£21,177	£38,114	1.482	£25,722
+ No age-based utility decrements	£15,743	1.431	£11,003	£31,369	1.499	£20,923	£38,114	1.505	£25,320
ERG revised base case	£15,743	1.431	£11,003	£31,369	1.499	£20,923	£38,114	1.505	£25,320
	2D/3D vs. PR								
	Incr. Costs	**Incr. QALYs**	**ICER**						
Base case from CS	£9,384	1.907	£4,920						
Re-infected patients return to their pre-SVR state	£10,759	1.710	£6,293						
+ SVR utility increment from clinical trials	£10,759	1.518	£7,089						
+ No age-based utility decrements	£10,759	1.542	£6,977						
ERG revised base case	£10,759	1.542	£6,977						

7 OVERALL CONCLUSIONS

The conclusion from the EBR/GZR trials is that EBR/GZR has high SVR rates, especially for patients with GT1a and GT1b. In addition, EBR/GZR has a relative favourable safety and tolerability profile, especially when compared with P and/or RBV containing regimens.

Comparator data (for SVR12 and AEs) were provided by single arms of randomised controlled trials (RCTs), or non-RCTs. Although reported baseline characteristics appear similar between intervention and comparator trials, the possibility that other factors differed across trials cannot be ruled out. The ERG has serious problems with the methodology of both types of evidence synthesis performed by the company and considers the outcomes of these analyses therefore as unreliable.

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent and is fairly in line with the decision problem specified in the scope.

The findings of the ERG base-case analysis are generally in line with those from CS. For GT1a and GT4 populations, ICER (compared to PR) values for EBR/GZR were around £8,000-£9,000 per QALY gained for cirrhosis patients and around £11,000-£12,000 per QALY gained for non-cirrhosis patients. For GT1b, in the TN and NC populations, ICER (compared to PR) was almost £13,000 per QALY gained, whereas for the other GT1b populations, ICER values were around £8,000 per QALY gained.

From the full incremental analysis, EBR/GZR appeared to be cost effective only in GT1a TN C, GT1a TE C and GT4 TE C populations. In GT4 TN C population, EBR/GZR resulted in an ICER around the £20,000 per QALY gained threshold, and in all other populations, EBR/GZR was either dominated by the other cost effective interventions, or the ICER values compared to the other cost effective interventions were above the £20,000 per QALY gained threshold.

Findings from the PSA and scenario analyses were also comparable to the CS base case. Choice of the evidence synthesis approach and using GT4 specific data for GT4 subgroup had significant impacts on the ICER across all groups.

In general EBR/GZR seems to be cost effective compared to PR in all presented subgroups. Only when the time horizon is five or 10 years EBR/GZR was not cost effective in all populations, and when the age-based disease progression transition probabilities were used, EBR/GZR stopped to be cost effective in non-cirrhotic populations compared to PR. If all other comparators were considered in the full incremental analysis, EBR/GZR is cost effective only in GT1a TN C, GT1a TE C and GT4 TE C populations (both in the analyses from the company and the ERG). However, these results should be interpreted with precaution, as these results were based on list prices and treatment effectiveness parameters were based on questionable assumptions/methods.

7.1 Implications for research

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 EBR/GZR 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.

Also, recently, it was advocated in the literature that lower cost effectiveness thresholds should be considered for new chronic HCV treatments, given the potential health system impact of reimbursing these drugs.[115] If this opinion is shared among the decision makers, methods to determine this threshold would be needed.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Grazoprevir–elbasvir for treating chronic hepatitis C [ID842]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 8 July 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

General comment:

MSD would like to thank the ERG group, for a well-structured, clear, and concise report. The format of this report made it clear for MSD to review comments and relate back to the EBR/GZR submission.

Issue 1 Compound name

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11, 17 and 23 (throughout document) "The company's submission (CS) presents an evaluation of the clinical effectiveness and cost effectiveness of grazoprevir/elbasvir (EBR/GZR) for the treatment of chronic hepatitis C"	MSD proposes to use consistently the acronym EBG/GZR in the report. Exception can be made when referring to the original studies.	Please note that the official compound name acronym is EBR/GZR (elbasvir/grazoprevir).	The ERG report uses consistently the acronym: EBR/GZR. For the full name of the intervention we have used the name as specified in the NICE final scope: grazoprevir-elbasvir. Therefore, we will leave the report as it is.

Issue 2 Clinical effectiveness RCT evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11 "six out of eight EBR/GZR studies are RCTs" "From the six included EBR/GZR RCTs, two studies have no relevant control arms" "The EBR/GZR trials included patients with GT1, 3, 4 and 6; treatment naïve, experienced and mixed patient populations; mixed fibrosis status; and patients with 'no HIV' (C-EDGE TN, C-SURFER and C-EDGE H2H), chronic	 "seven out of eight EBR/GZR studies are RCTs" "From the seven included EBR/GZR RCTs, three studies have no relevant control arms" "The EBR/GZR trials included patients with GT1, 3, 4 and 6; treatment naïve, experienced and mixed patient populations; mixed fibrosis status; and patients with 'no HIV' (**C-SCAPE**, C-EDGE TN, C-SURFER and C-EDGE	 MSD would like to clarify that on page 58 of the CS 7 RCTs are described. C-EDGE TN; C-EDGE TE; C-SURFER; C-WORTHY; C-SCAPE; C-EDGE CO-STAR; C-EDGE H2H C-SCAPE seems to have been omitted. The CSR states that C-SCAPE arms B2 and B3 were randomised in a 1:1 ratio to receive either EBR/GZR 12 weeks (arm of interest) or EBR/GZR +RBV 12 weeks (not relevant to license). The	C-SCAPE was omitted because it was not a fully randomised study. Only 2 out of 4 arms were randomised. Therefore, we did not considered it an RCT.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
kidney disease (C-SURFER), or 'on opiate substitution therapy' (C-EDGE CO-STAR)."	H2H), chronic kidney disease (C-SURFER), or 'on opiate substitution therapy' (C-EDGE CO-STAR)."	arm of interest reports 11 patients, 10 of which have GT4 infection and are described as treatment naïve.	
Page 29 "From the six included EBR/GZR RCTs, two studies have no relevant control arms…"	"From the seven included EBR/GZR RCTs, three studies have no relevant control arms…"	MSD ask that the report be amended to reflect the RCTs reported throughout. (As per comment relating to the ERG report page 11).	See above
Page 31 Table 4.2 included studies	C-SCAPE is missing from the table and should be included as this is an open label randomised trial for treatment arms B2 and B3.	C-SCAPE treatment arms of interest were randomised as per earlier comments	Table 4.2: C-SCAPE is listed as no. 32: a non-randomised EBR/GZR study
Page 42 Table 4.4 C-EDGE H2H Population column states GT1, 4, and 6	GT 1 and 4	MSD would like to confirm that C-EDGE H2H was designed to enrol patients with GT1, 4 and 6 infections, as per the comments of table 4.4. However, no patients with GT6 infection were enrolled. Therefore, MSD would suggest stating GT1 and GT4 to be clearer regarding the population column.	Not a factual error.

Issue 3 Statistical analysis (NMA methodology)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 62 "Table 4.2…"	Table 4.12	MSD were unclear, if the ERG meant tables within section 4.2, including tables 4.12 – 4.14	We do not understand the question. Table 4.2 is not mentioned on page 62 in our version. It is mentioned at the top of page 58 – there 'Table 4.2' is correct.
Page 62 "…This was done by adding all the data, so the numerator was the sum of the events and the denominator was the sum of the number of patients. This is not strictly a meta-analysis as it ignores differences in the sizes of the studies and treats them all equally in the pooled result. If the data had been combined using a meta-analysis then some form of weighting would have been used so the results from larger studies were given more weight in the analysis"	This text should be removed as this is not factually correct. The CS did take into consideration the weighting of trial size, and followed a meta-analytic approach.	The ERG appears to have misunderstood how the pooled proportions were calculated, and this explains why they were not able to recreate the pooled proportions presented in the CS (Page 84 of ERG report). Rather than simply adding the number of patients and events from relevant trial arms for each comparator, a meta-analytical approach was applied using the R function metaprop, with inverse variance weighting and no transformation	This is also on page 58 of the ERG report. This is not a factual error. There is no mention of metaprop in the CS or appendices. The methods clearly state in sections 4.10.8 (page 129) and Appendix 8 (page 174) that "All study arms pertaining to a given regimen were combined to obtain pooled proportions, where the numerator is the sum of events and the denominator is the sum of the number of patients."
Page 62/63 "Calculating the RR based on pooled proportions in this way is incorrect as it is ignoring the randomisation within the trials" "Methods of meta-analysis should respect randomisation, so breaking	MSD asks that both sentences are removed or contextualised to reflect the HCV therapeutic area. Suggested text if not removed: "The CS in an attempt to utilise the HCV evidence-base calculated RR based on	The assertion that breaking randomisation through a naïve comparison of single arms from different trials is at odds with the current regulatory approach to clinical trial design for direct-acting	This is on page 58/59 of the ERG report. This is not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
randomisation by using single arms from different trials is not an appropriate approach and also ignores possible heterogeneity between the trials in terms of populations, settings, treatments and timings and methods of outcome measurement"	pooled proportions from multiple single arm/ non-comparative trials, which follows a precedent accepted by both the FDA and EMA for treatment of hepatitis C."	antivirals for hepatitis C. Both the FDA and EMA accept the use of historical controls where clinically appropriate, as is the case where treatments are known to be highly efficacious and there is limited scope for effect modification based on patient characteristics. The naïve comparisons included within the CS can be thought of as akin to such a comparison, with existing trial arms acting as historical controls.	
Page 64 "…there are more than two underlying conditions, clinical and statistical heterogeneity between the trials should also be addressed, which have not been considered in the submission."	This text should be removed. MSD did take into account clinical and statistical heterogeneity when possible within the NMA. MSD suggests that the text could be updated to reflect the imputed PR control arms that were matched to the relevant single arm trials they were imputed for. This was explained within the CS, as was planned sensitivity analysis, when possible for trial heterogeneity.	The ERG asserts that clinical and statistical heterogeneity were not considered. However, these were precisely the reasons that led to the decision to carry out NMAs on the specific subgroups as an adjunct to the naïve comparisons. As previously stated, the naïve-comparisons were not able to account for heterogeneity across studies. The NMA allowed us to examine what impact such heterogeneity might have, yet required imputation of control arms in order to be run. The large degree of concordance across the two analytical approaches provides at least some indication of the magnitude to which any difference between studies do alter outcomes.	This is on page 60 of the ERG report. We agree that performing the analyses for specific subgroups was an attempt to control for clinical heterogeneity. However, having to impute a high proportion of the control arms in order to run the NMA in the first place, means that the NMA is not an appropriate analysis for assessing between trial heterogeneity. Imputing control arms is not a substitute for evaluating whether the trials were sufficiently clinically similar to be pooled. Section 4.10.8 (page 128) states that "As discussed above, the NMA was conducted on groups with clearly defined characteristics. In all but a handful of included

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
			trials, these groups were a subgroup within the population of the trial or arm overall. This meant it was not possible to accurately compare the patient characteristics across these specific subgroups, as information was generally only presented at the arm level." Statistical heterogeneity was not evaluated in the submission as there are no forest plots or reporting of I-squared values, or statistical tests of heterogeneity. If the R function metaprop was used to pool proportions (as stated for the previous comment) then this provides the heterogeneity Q statistic, as well as the between study variance. Both of these are measures of statistical heterogeneity but were not reported alongside the pooled proportions for each treatment.

Issue 4 Validation status of the cost-effectiveness analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P135: "In the CS, no details were given concerning the validation by an external health economist as well as by the clinical experts. The company did not provide these details despite the request of the ERG, Furthermore, the ERG requested the filled in version of the checklist provided in Appendix 23 of the CS, however the company did not provide this either"	MSD suggests amending the paragraph as follows: "In the CS, limited details were given concerning the validation by an external health economist as well as by the clinical experts; however the company provided additional details during the clarification questions relating to the content of both meetings." Please also amend paragraph 3 page 163	Please note that, in the absence of a questionnaire given at the meeting with the health economist expert, MSD provided an overall description of the validation meeting as well as the checklist used for the internal validation of the model as CiC information as part of Appendix 23 of the submission. In the absence of questionnaire given during the meeting with clinical experts, MSD provided a detailed description of discussion within the clarification questions.	The ERG disagrees with the proposed amendments. In the CS, just brief information was provided regarding the validation, and no details. The answers to the questions in the clarification letter were repetition of what was written in the CS.

Issue 5 Summary of the company's submitted economic evaluation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P73: "SVR F0-F3: F0-F3" "PLT: after first year of liver"	MSD suggests amending the text as follows: "SVR F0-F3" "PLT: after first year of liver transplant"	Missing text within the ERG report compared with the CS.	The ERG does not agree with the first proposed amendment, because SVR F0-F3 corresponds to being F0-F3 and achieving SVR at the same time. The ERG agrees with the second proposed amendment, and has

			added “transplant” at the end of “PLT: after first year of liver”: “PLT: after first year of liver transplant”

Issue 6 Model structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P80: “In the health economic model, it was assumed that after patients reach SVR, a re-infection would mean that they re-start the course of the disease from F0, which is the health state with no fibrosis”	MSD suggests amending the sentence as follows: “In the health economic model, it was assumed that after non-cirrhotic patients reach SVR, a re-infection would mean that they re-start the course of the disease from F0, which is the health state with no fibrosis”	As per earlier comments, MSD has justified the subgroups presented within the submission i.e. anticipated EU license and relevant comparisons made with NICE TA recommendations	The ERG agrees with the amendment and has added “non-cirrhotic” to the sentence.
P136: “As described in Section 5.2.3, the ERG has the opinion that a modelling approach, in which patients return to the fibrosis stage they were in before reaching SVR, would reflect the clinical prognosis better than the approach followed in CS, in which patients always return to “no fibrosis” (F0) stage, after being re-infected.”	MSD suggests amending the sentence as follows: “As described in Section 5.2.3, the ERG has the opinion that a modelling approach, in which non-cirrhotic patients return to the fibrosis stage they were in before reaching SVR, would reflect the clinical prognosis better than the approach followed in CS, in which patients always return to “no fibrosis” (F0) stage, after being re-infected”	Missing text.	The ERG agrees with the amendment and has added “non-cirrhotic” to the sentence.

Issue 7 HRQoL data included in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P100: "Once age-based utilities are lower the age-based utilities should be used"	MSD suggests amending the wording so as to make it clear for the reader.	MSD does not understand the comment.	The ERG agrees with the proposed amendment and has replaced the sentence with the following: "Once age-based population utilities become lower than the health state specific utilities, the age-based population utilities should be used"

Issue 8 HRQoL data included in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P100: "The company could have based the health state utilities only on patients below the age of 40 (45 for TE patients), and then include age-based utility decrements in a linear fashion from that age onwards"	MSD suggests removing the sentence.	As explained page 194 of the submission, patients enter the model at the age of 40 or 45.	The ERG does not agree with the proposed amendment, but instead suggests replacing the sentence with the one below for clarification: "The company could have based the health state utilities only on the average of patients below the age of 40 (45 for TE patients), as utility does not decline between 25 and 45 years, and then include age-based utility decrements in a linear fashion from that age onwards, which would prevent the double counting issue discussed above. This would require patient-level utility data from the Wright et al.

			study.”

Issue 9 Base case incremental cost-effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P136: “Once the GT1a patients with polymorphisms have been detected, they will receive 16 weeks of EBR/GZR plus ribavirin instead of the 12 weeks assumed in the current model.”	“Once the GT1a patients with polymorphisms have been detected, at the discretion of the treating clinician (who should consider 16 weeks therapy) they may receive 16 weeks of EBR/GZR plus ribavirin instead of the 12 weeks assumed in the current model.”	MSD would like to reflect the anticipated label of EBR/GZR and the use of 16 weeks as per the SPC. This states that clinicians should consider 16 weeks therapy + RBV. The wording of the ERG report suggests that all patients will receive 16 weeks therapy, and this is not the case.	The ERG agrees with the proposed amendment and has replaced the sentence with: “Once the GT1a patients with polymorphisms have been detected, at the discretion of the treating clinician (who should consider 16 weeks therapy) they may receive 16 weeks of EBR/GZR plus ribavirin instead of the 12 weeks assumed in the current model.”

Issue 10 Conclusions of the cost effectiveness section

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P161: “BOC/PR and TVR/PR and SMV/SOF treatments were not considered as a comparator, as they were not part of the current clinical practice according to the company”	Please delete SMV/SOF throughout document as this not NICE recommended.	Please note that SMV/SOF is not recommended by NICE and was therefore not considered as a comparator.	The ERG does not agree with the proposed amendment because NICE was unable to make a recommendation for SMV/SOF, which is different from the case in which NICE guidance does not recommend SMV/SOF.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

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Grazoprevir–elbasvir for treating chronic hepatitis C

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
69	Text added: "transplant"
75	Text added: "non-cirrhotic"
96	Text added: "the average of" Text added: "as utility does not decline between 25 and 45 years," Text added: "which would prevent the double counting issue discussed above. This would require patient-level utility data from the Wright et al. study" Text added: "than the health state specific utilities,"
131-132	Text added: "at the discretion of the treating clinician (who should consider 16 weeks therapy)" "will" is replaced by "may" Text added: "non-cirrhotic"

	Approach	Source/Justification	Signpost (location in CS)
States and events	The model consists of 13 states. F0-F3 are non-cirrhotic states and F4 was considered as cirrhotic state. • F0: no fibrosis • F1: portal fibrosis without septa • F2: portal fibrosis with septa • F3: portal fibrosis with numerous septa without septa • F4: compensated cirrhosis • SVR F0-F3: F0-F3, achieved SVR after treatment • SVR F4: compensated cirrhosis, achieved SVR after treatment • DC: decompensated cirrhosis • HCC: Hepatocellular carcinoma • LT: First year of liver transplant • PLT: After first year of liver transplant • 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; patients with decompensated cirrhosis (or more severe health state) are not eligible for treatment. 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 achieved SVR are at risk of re-infection. Patients who reached F4 can progress to DC and HCC states, which may lead to liver transplantation and liver related death. Liver transplantation was divided into two categories (1st year of LT and post LT years).	Health states were based upon disease severity. The treatment determines the SVR, adverse event and discontinuation probabilities.	Section 5.2.2 (p. 187)
Comparators	Comparators differ for each of the considered subpopulation. EBR/GZR (EBR and GZR 12w; subpopulations 1-12) BSC (subpopulations: 2, 4, 6, 8, 10 and 12)	They are based on licensed indications and NICE recommendations.	Section 5.2.4 (p. 192)

after first year post liver transplant). All these post-cirrhosis states have differing excess risks of liver related death.

During the initial treatment phase of the model, patients receive antiviral drug therapy (first year). All treatment related outcomes are assumed to occur in the first year of the model. It is assumed that patients could not clear from their infection spontaneously and patients do not progress or die in during the treatment period. In the model, after a successful treatment, it is assumed that patients achieve SVR, and patients who do not achieve SVR are at the same risk of disease progression as untreated patients. Non-liver related death can occur in each state.

Non-cirrhotic patients who achieve SVR remain in the current health state unless re-infected. Cirrhotic patients who achieve SVR either can remain in the current health state or can progress onto more severe health states, and they are assumed to have an excess risk of DC and HCC. Patients who received liver transplant assumed to be at no risk of reactivation of HCV.

ERG comment: The model structure is conceptually similar to the models that were recently submitted in previous submissions.[89-91] The ERG thinks that even though the model structure reflects the key elements of the hepatitis C disease progression with and without treatment, there could be more suitable modelling types than a static Markov model. Dynamic modelling approaches could have incorporated the health effects in between individuals within a population by reflecting the effect of HCV treatment in preventing future transmissions. Hence, on a patient population level, the health benefits of more effective treatments with higher SVR rates may have been underestimated, however the magnitude of the underestimation can only be quantified by constructing a de-novo dynamic model.

The current model structure in the CS also only allows the comparison of a single course of treatment used immediately. 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. These aspects of the clinical practice were omitted in the model structure provided in the CS.[1]

In the health economic model, it was assumed that after non-cirrhotic patients reach SVR, a re-infection would mean that they re-start the course of the disease from F0, which is the health state with no fibrosis. This assumption implies that the liver damage caused by chronic hepatitis C is fully reversible once SVR is achieved. In the CS,[1] no evidence was provided to support this assumption. Furthermore, there is no clinical consensus on the full reversibility of fibrosis caused by hepatitis C, and this approach is against the previous modelling assumptions used in previous NICE TAs (e.g. TA 365[91]). Finally, the ERG's clinical experts suggested that this assumption of fully reversal of fibrosis after SVR might not be always plausible (Personal communication Dr Ryder, 7 June 2016). Therefore, in the additional analyses conducted by ERG, it is assumed that after SVR re-infection, the re-infected patient begins the disease course from his/her pre-SVR health state, and not always from "no fibrosis" state.

literature used in the model. The company states in the response to the clarification letter[65] that these deviating utilities might be due to differences in geographic regions and disease backgrounds. According to the clinical expert consulted by the ERG (Personal communication Dr Ryder, 7 June 2016), these differences might also be due to changes in patient perspectives over time – where hepatitis C used to be incurable for many patients, the disease can nowadays be managed well with new DAA therapies. As such, the mental impact for patients might be less than before, and quality of life at the start of treatment might be higher. This remark is particularly relevant as the utility values used in the model originate from EQ-5D questionnaires that were completed back in 2002.[67] The utility values for more advanced liver disease originate from data collected in 1998.[108]

Unfortunately, it was not possible for the ERG to construct a scenario using the EQ-5D utilities reported in the CS (Tables 70 and 71) instead of the published utilities, since these utilities were not available per separate health state (F0-F4). However, the estimate of the utility increment associated with SVR was derived from the European patients in the EBR/GZR trials, and was reported in the CS,[1] henceforth the ERG believes that this estimate is a better reflection of the current UK clinical practice.

The EQ-5D-5L instrument was used to elicit patients' quality of life in the RCTs. The EQ-5D-5L value set for the UK should therefore have been used to compute utilities. However, trial-based utilities were calculated using a three level crosswalk algorithm in the CS.[1] Relevant and significant differences exist between this three level crosswalk and the five level value set. The ERG requested trial-based utilities recalculated using the EQ-5D-5L value set. The company declined to provide these utilities, stating that they anticipated that the absolute difference would not be affected.[65] No evidence for this expectation was provided.

The approach used to estimate treatment-specific utility decrements does not seem suited for disentangling the effect of treatment and disutilities from adverse events. Alternatively, the company could have compared the utility value for those patients that had experienced adverse events to the utility values of those patients that did not experience adverse events. However, as the prevalence of adverse events relative to placebo is quite low, the ERG does not expect that using another approach would have resulted in substantially different outcomes in relation to EBR/GZR specific disutilities.

In the cost effectiveness model, quality of life decreases with age. Conceptually, including age-based utility decrements is correct. However, the ERG is not convinced that the approach used by the company is correct. By subtracting utility decrements from the health state utilities, double counting might occur. Age decrements are applied from the age of 40 (45 for TE patients) onwards. Health state utilities were derived from a subset of a larger population of patients that are aged between 21 and 67.[67] As most of these patients are over the age of 40, the impact of age on HRQoL is (implicitly) already taken into account in their utility values. Several alternative approaches could have been used to correctly include age-based decrements. The company could have based the health state utilities only on the average of patients below the age of 40 (45 for TE patients),), as utility does not decline between 25 and 45 years, and then include age-based utility decrements in a linear fashion from that age onwards, which would prevent the double counting issue discussed above. This would require patient-level utility data from the Wright et al. study. However, this would clearly reduce the sample size. Alternatively, health state utility values can be used until age-based utilities from the general UK population are lower. Once age-based utilities are lower than the health state specific utilities, the age-based utilities should be used. In this respect, the implicit assumption would be that HCV patients would always have lower or equal utilities as the general population. Based on the utility values of the health states relative to the utility value of the general UK population, this would not have a large impact on the outcomes. In the ERG base-case scenario, the age-based utility decrements are not included to avoid double counting and to

5.2.11 Model validation and face validity check

In the CS, it was mentioned that the model approach and inputs had been validated by an external health economist with expertise in hepatitis C, who was described as a leading expert in health economics practice and methodology development in the UK for the economic evaluation of HCV. It was also mentioned that the accuracy of the implementation and programming of the model was verified via internal quality control processes using an internal quality control checklist, which was given in Appendix 23 of the CS.[56]

ERG comment: In the CS, no details were given concerning the validation by an external health economist as well as by the clinical experts. The company did not provide these details despite the request of the ERG.[65] Furthermore, the ERG requested the filled in version of the checklist provided in Appendix 23 of the CS,[56] however the company did not provide this either.

There were also no other validation efforts, and the ERG asked the company to conduct additional validation exercises such as cross-validation, validation against external data, validation against internal data. However, in the response to the clarification letter, the company stated (B26[65]): "*MSD believes all necessary validation of the model has been conducted and does not believe that further validation would provide additional value to the model.*"

The ERG disagrees strongly with the company's statement, and thinks that validation efforts suggested in the clarification letter constitute one of the most important part of the company evidence, and not providing any details on the validation is a serious violation of good modelling practice.[114]

The ERG had a quick check with the in-house quality assurance checklist to confirm technical validity of the model and no serious errors were found. The total QALY estimates from the previous TAs (e.g. TA 364)[90] of a common intervention like PR were comparable with those from the CS. However further than this, the ERG cannot make any other conclusive remarks on the validation status of the cost effectiveness evidence submitted by the company.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 ERG base-case analyses

Based on the remarks raised in Section 5.2 of this report, the ERG defined a new base-case analysis. Unfortunately, one issue could not be addressed quantitatively, i.e. the 16 week treatment duration for patients with GT1a and the presence of specific NS5A RAVs causing at least a five-fold reduction in activity of elbasvir. In order to select these patients, all patients would first need a test to assess the presence of any polymorphisms that could impact treatment effectiveness. Thus, for all patients entering the model, the costs of such test should be added.

Once the GT1a patients with polymorphisms have been detected, at the discretion of the treating clinician (who should consider 16 weeks therapy) they may receive 16 weeks of EBR/GZR plus ribavirin instead of the 12 weeks assumed in the current model. Thus, overall treatment costs will go up. At the same time, the number of patients reaching SVR will increase, as the prolonged intervention will lead to a higher overall SVR rate in GT1a patients. This will in turn lead to more life years and more QALYs. At the same time, costs will be saved by having fewer patients in the more severe (and costly) health states. Thus, including testing into the model will have impact on almost every part of the model outcomes, and it is currently not possible to predict what the net effect will be on the cost effectiveness of EBR/GZR. In order to quantify this effect, it would be necessary to have

SVR rates, discontinuation rates and AE rates separated out for patients with a negative test result receiving 12 weeks of treatment and patients with a positive test result receiving 16 weeks of EBR/GZR plus ribavirin.

All other relevant issues discussed in Section 5.2 could be quantified, so a new ERG base-case was defined based on the following adjustments:

- *Model structure adjustment to allow that after reinfection, patients return to the fibrosis stage they had been just before SVR.*

As described in Section 5.2.3, the ERG has the opinion that a modelling approach, in which non-cirrhotic patients return to the fibrosis stage they were in before reaching SVR, would reflect the clinical prognosis better than the approach followed in CS, in which patients always return to "no fibrosis" (F0) stage, after being re-infected. Therefore, in the ERG base-case, the former approach was selected as the ERG base-case and the latter approach (CS base-case) explored as an ERG scenario analysis.

- *Using SVR related utility increments from the EBR/GZR clinical trials.*

As described in Section 5.2.7, the ERG, believes that the fibrosis health state and SVR related utility increment estimates from Wright et al., 2006,[67] which were used in the company's base-case, may not reflect the current UK clinical practice, since these estimates are older than 10 years. Ideally, the ERG would prefer to use both fibrosis disease stage (F0-F4) utility and SVR related utility increment estimates derived from the EBR/GZR clinical trials. However, the former (fibrosis disease stage utility) estimates were not available to the ERG. The company provided an estimate for the SVR related utility increment based on European patients from the EBR/GZR clinical trials. This estimate (0.03) is a bit lower than the Wright et al., 2006[67] estimate (0.05). Despite the fact that this estimate from the EBR/GZR clinical trials was not derived from UK patients and despite the presence of some methodological issues discussed in Section 5.2.7 (such as not using EQ-5D-5L value sets), the ERG still believes that this would be a more plausible estimate for the SVR related utility increments in the ERG base-case, since it is much more recent. Therefore in the ERG base-case, SVR related utility increments from the EBR/GZR clinical trials were applied, whereas the estimate from Wright et al., 2006 (0.05)[67] is applied in one of the ERG scenarios.

- *Age-based utility decrements were removed from the base-case analyses*

As described in Section 5.2.7, the ERG expressed its concerns on the potential double counting while incorporating the age-based utility decrements in the CS model and on the implementation of decrements as a linear function. Furthermore, the ERG noticed that these age based utility decrements were generally not included in previous STAs, except for TA364[90]. In the ERG base-case, it was decided not to include age-based utility decrements, whereas in one of the ERG scenarios, age-based utility decrements were included.

The ERG decided to keep other assumptions of the base-case analyses from the model submitted by the company.

The ERG base-case pairwise incremental cost effectiveness results for comparisons of EBR/GZR and its relevant comparators versus PR across all the different populations are listed in Table 5.42 for GT1a, in Table 5.43 for GT1b and in Table 5.44 for GT4 patients. Next to the pairwise incremental results, full incremental results are also provided in Tables 5.45 to Tables 5.47.

The findings of the ERG base-case analysis are generally in line with those from the CS. For GT1a and GT4 populations, the ICER (compared to PR) values for EBR/GZR were around £8,000-£9,000