Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C

SHTAC ERG additional analyses

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Table of contents

Contents

Introduction 3
Section 1: Genotype 1, treatment-naive, interferon-eligible patients 4
Genotype 1a, treatment-naive, interferon-eligible patients 8
Genotype 1b, treatment-naive, interferon-eligible patients 10
Section 2: Genotype 1, treatment-experienced, interferon-eligible patients 12
Genotype 1a, treatment-experienced, interferon-eligible patients 15
Genotype 1b, treatment-experienced, interferon-eligible patients 17
Section 3: Genotype 4, interferon-eligible patients 19

Table of tables

Table 1 GT1, treatment-naive, IFN-eligible patients, all fibrosis stages 6
Table 2 GT1, treatment-naive, IFN-eligible patients, by cirrhosis status 7
Table 3 GT1a, treatment-naive, IFN-eligible patients, all fibrosis stages 8
Table 4 GT1a, treatment-naive, IFN-eligible patients, by cirrhosis status 9
Table 5 GT1b, treatment-naive, IFN-eligible patients, all fibrosis stages 10
Table 6 GT1b, treatment-naive, IFN-eligible patients, by cirrhosis status 11
Table 7 GT1, treatment-experienced, IFN-eligible patients, all fibrosis stages 13
Table 8 GT1, treatment-experienced, IFN-eligible patients, by cirrhosis status 14
Table 9 GT1a, treatment-experienced, IFN-eligible patients, all fibrosis stages 15
Table 10 GT1a, treatment-experienced, IFN-eligible patients, by cirrhosis status 16
Table 11 GT1b, treatment-experienced, IFN-eligible patients, all fibrosis stages 17
Table 12 GT1b, treatment-experienced, IFN-eligible patients, by cirrhosis status 18
Table 13 GT4, non-cirrhotic, IFN-eligible patients 20
Table 14 GT4, cirrhotic, IFN-eligible patients 21

Introduction

SHTAC conducted additional analyses to derive cost effectiveness estimates for non-cirrhotic and cirrhotic patients (for each HCV genotype and genotype subgroup) following discussions at the pre-meeting teleconference on 18th March. The additional analyses have been conducted using the company model and have applied the company's base case assumptions, unless otherwise stated.

The first table in each section of this report repeats the analyses presented in the company base case (Table 1 reports the base case for GT1, treatment-naive, IFN-eligible patients, Table 7 reports the base case for GT1, treatment-experienced, IFN-eligible patients and Table 13 reports the base case for GT4, treatment-naive, IFN-eligible patients and treatment-experienced, IFN-eligible patients). Subsequent tables in each section report cost effectiveness results for each patient population for non-cirrhotic and cirrhotic patients separately and, in the case of GT1 patients, by genotype sub-group and by cirrhosis status. Treatments listed in all the tables are ranked in terms of increasing cost.

A column has been added to the right of each table which shows a plot of incremental costs and QALYs which is intended to clarify which comparators are included in the incremental analysis and to clearly indicate where relevant comparators have been excluded due to extended dominance. The abbreviations used in the figures are as follows:

PR = PegIFN+RBV;
BOC = Boceprevir+ PegIFN+RBV;
TEL = Telaprevir+PegIFN+RBV;
SOF = Sofosbuvir+PegIFN+RBV;
3D±RBV = (Ombitasvir/paritaprevir/ritonavir with dasabuvir) with or without ribavirin
2D+RBV = Ombitasvir/paritaprevir/ritonavir with ribavirin

Section 1: Genotype 1, treatment-naive, interferon-eligible patients

As indicated in the Introduction, Table 1 repeats the base case analysis for GT1 patients in the CS, which includes a combined population of non-cirrhotic and cirrhotic (10% cirrhotic) GT1a and GT1b (68.8% GT1a) patients. Table 2 and Table 3 report cost effectiveness results, calculated by the ERG, from the company model for non-cirrhotic and cirrhotic patients separately. Total costs are higher for cirrhotic patients than for non-cirrhotic patients due to a higher proportion of the cirrhotic cohort progressing to more advanced liver disease. For example, the model estimates that for a cohort of cirrhotic patients, treated with 3D, 14% will develop decompensated disease and 37% will develop hepatocellular carcinoma. The equivalent values for non-cirrhotic patients are 5% and 2%, respectively. For a cohort of cirrhotic patients, treated with PegIFN+RBV, the model estimates 46% will develop decompensated disease and 31% will develop hepatocellular carcinoma, while the equivalent values for non-cirrhotic patients are 16% and 7%, respectively. These differences in progression to advanced liver disease between cirrhotic and non-cirrhotic patients translate to health state costs which are £20,950 for GT1 cirrhotic patients treated with 3D, compared with £4,131 for non-cirrhotic patients, and £36,042 for GT1 cirrhotic patients treated with PegIFN+RBV, compared with £12,151 for non-cirrhotic patients.

Total QALYs estimated in cohorts of cirrhotic patients are lower than for cohorts of non-cirrhotic patients. However the QALY gains (incremental QALYs) modelled for anti-viral treatment are generally greater for cirrhotic patients than for non-cirrhotic patients, since a greater proportion of patients who do not achieve SVR would be expected to progress to advanced liver disease.

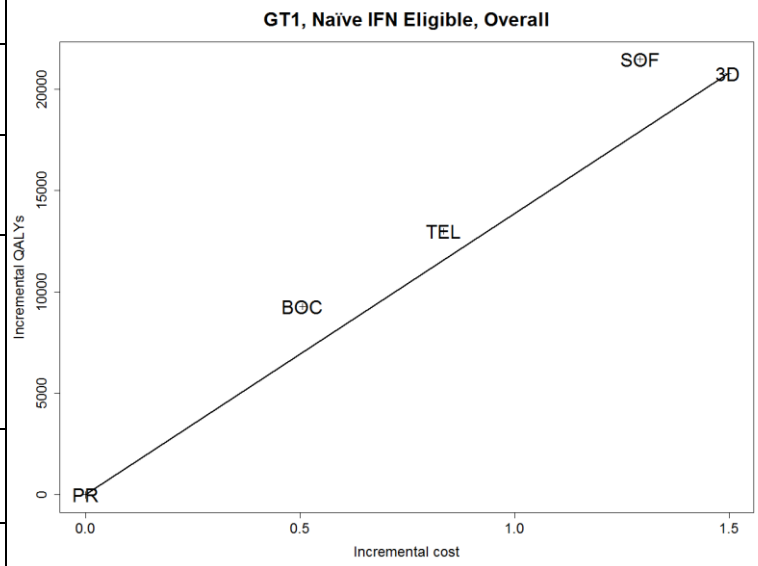
Treatment costs for GT1a HCV cirrhotic patients treated with 3D+RBV are also higher since treatment duration for these patients with is 24, rather than 12 weeks. For patients with GT1a HCV estimated treatment costs with 3D+RBV in the model increase from £35,607 for non-cirrhotic patients, to £69,900 for cirrhotic patients. Non-cirrhotic patients are treated with 3D, while all other GT1 patients receive 3D in combination with ribavirin. Treatment costs for other regimens do not vary by cirrhosis status.

All comparators to 3D±RBV, other than PegIFN+RBV, are excluded (by dominance or extended dominance) from the incremental analysis for the combined population of GT1 patients, including both cirrhotic and non-cirrhotic patients and when including only non-cirrhotic patients. However, Sofosbuvir+PegIFN+RBV is included in the analysis for cirrhotic patients (see Table 2). The ICER for cirrhotic GT1 patients is less favourable than for non-cirrhotic patients.

The incremental analysis for GT1a patients mirrors the results shown for the combined population of GT1 patients. The ICER for cirrhotic patients treated with 3D+RBV (compared with Sofosbuvir +PegIFN+RBV) is less favourable than for non-cirrhotic patients (3D+RBV compared with PegIFN+RBV), see Table 4. This reflects the higher treatment cost for 3D+RBV in GT1a patients with cirrhosis, resulting from their longer duration of treatment. In contrast, for GT1b patients the ICER for cirrhotic patients is more favourable than for non-cirrhotic patients. Incremental costs (relative to PegIFN+RBV) are lower and QALY gains are higher for cirrhotic GT1b patients treated with 3D+RBV than for non-cirrhotic patients treated with 3D alone, see Table 6.

Table 1 GT1, treatment-naive, IFN-eligible patients, all fibrosis stages

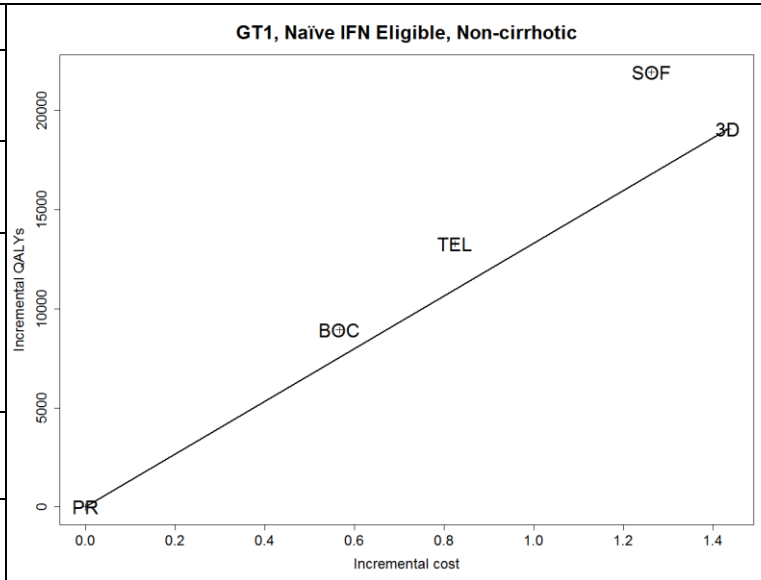
Genotype 1 (68.8% GT1a), treatment-naive, interferon-eligible, all stages of fibrosis (mild, moderate and compensated cirrhosis)					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	22,872	13.72	NA		
Boceprevir+ PegIFN+RBV	32,147	14.22	9,275	0.50	Extended dominance
Telaprevir+ PegIFN+RBV	35,887	14.55	13,014	0.83	
3D±RBV [a]	43,624	15.21	20,752	1.50	13,864
Sofosbuvir+ PegIFN+RBV	44,337	15.01	713	-0.21	Dominated



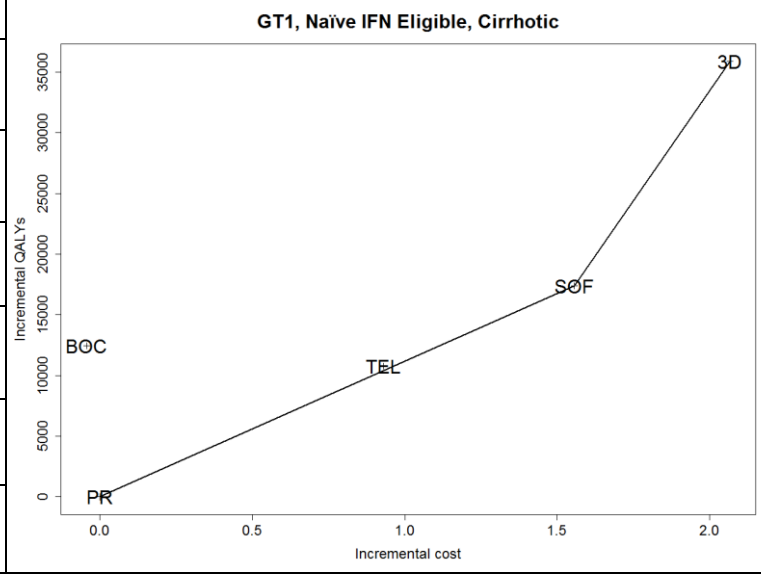
[a] Non-cirrhotic patients GT1b HCV are treated with 3D alone while all other GT1 patients receive 3D in combination with ribavirin

Table 2 GT1, treatment-naive, IFN-eligible patients, by cirrhosis status

Genotype 1 (68.8% GT1a), treatment-naive,interferon-eligible, non-cirrhotic)					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	20,483	14.33	NA		
Boceprevir+ PegIFN+RBV	29,404	14.90	8,921	0.57	Extended dominance
Telaprevir+ PegIFN+RBV	33,748	15.16	13,265	0.82	
3D±RBV	39,556	15.77	19,073	1.43	13,306
Sofosbuvir+ PegIFN+RBV	42,400	15.59	2,843	-0.17	Dominated



Genotype 1 (68.8% GT1a), treatment-naive, interferon-eligible, cirrhotic)					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	44,374	8.18	NA		
Telaprevir+ PegIFN+RBV	55,132	9.11	10,757	0.93	Extended dominance
Boceprevir+ PegIFN+RBV	56,827	8.13	12,453	-0.04	Dominated
Sofosbuvir+ PegIFN+RBV	61,777	9.73	17,402	1.56	11,182
3D+RBV	80,238	10.24	18,461	0.51	36,139



Genotype 1a, treatment-naive, interferon-eligible patients

Table 3 GT1a, treatment-naive, IFN-eligible patients, all fibrosis stages

Genotype 1a, treatment-naive, interferon-eligible, all stages of fibrosis (mild, moderate and compensated cirrhosis)					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	23,305	13.64	NA		
Boceprevir+ PegIFN+RBV	32,905	14.09	9,601	0.45	Extended dominance
Telaprevir+ PegIFN+RBV	36,378	14.47	13,073	0.82	
Sofosbuvir+ PegIFN+RBV	44,064	15.06	20,760	1.41	
3D+RBV	45,110	15.18	21,805	1.54	14,199

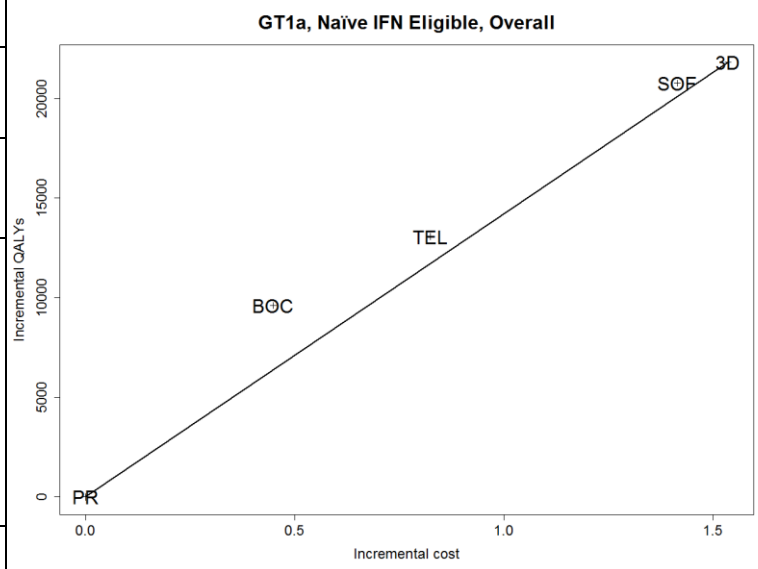
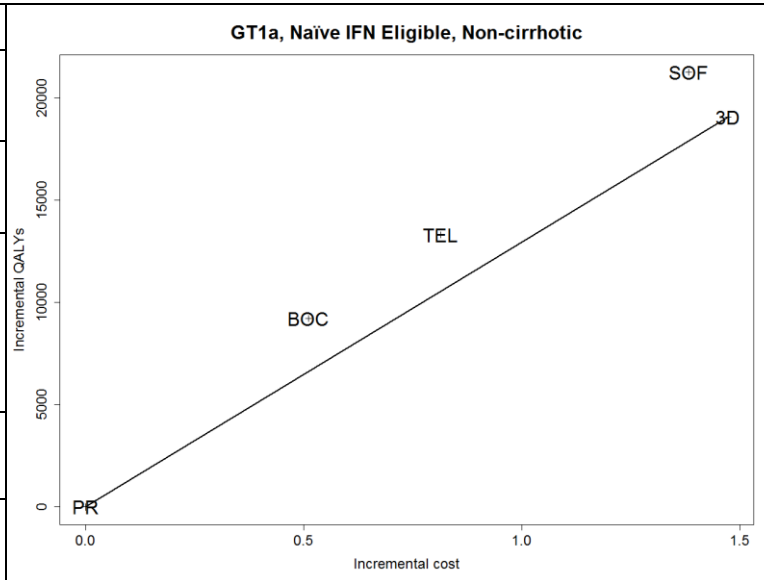


Table 4 GT1a, treatment-naive, IFN-eligible patients, by cirrhosis status

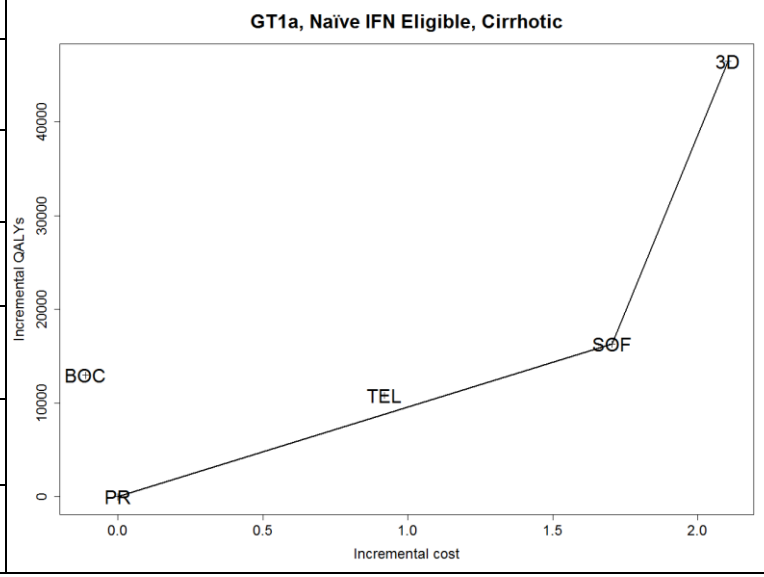
Genotype 1a, treatment-naive, interferon-eligible, non-cirrhotic

	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	20,888	14.26	NA		
Boceprevir+ PegIFN+RBV	30,114	14.77	9,226	0.51	Extended dominance
Telaprevir+ PegIFN+RBV	34,208	15.07	13,320	0.81	
3D+RBV	39,955	15.73	19,067	1.47	12,949
Sofosbuvir+ PegIFN+RBV	42,144	15.64	2,189	-0.09	Dominated



Genotype 1a, treatment-naive, interferon-eligible, cirrhotic

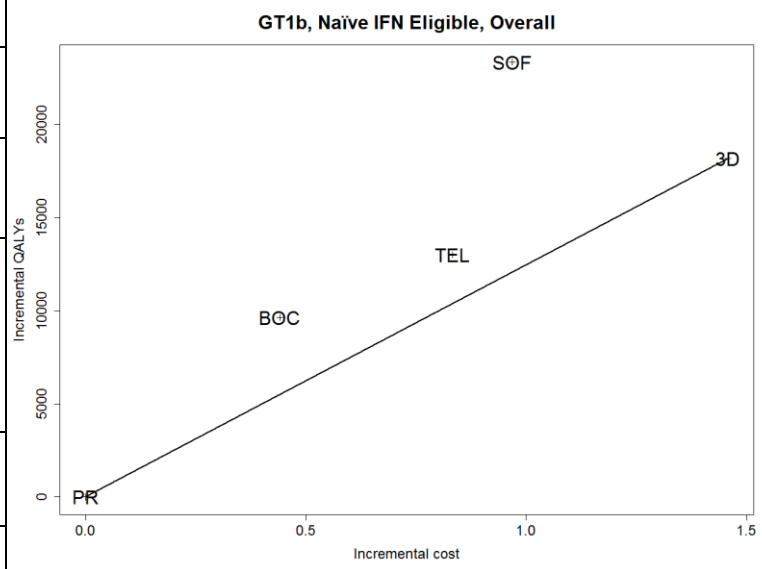
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	45,057	8.08	NA		
Telaprevir+ PegIFN+RBV	55,907	9.00	10,850	0.92	Extended dominance
Boceprevir+ PegIFN+RBV	58,024	7.97	12,967	-0.11	Dominated
Sofosbuvir+ PegIFN+RBV	61,347	9.79	16,290	1.70	9,555
3D+RBV	91,507	10.19	30,161	0.40	75,360



Genotype 1b, treatment-naive, interferon-eligible patients

Table 5 GT1b, treatment-naive, IFN-eligible patients, all fibrosis stages

Genotype 1b, treatment-naive, interferon-eligible, all stages of fibrosis (mild, moderate and compensated cirrhosis)					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	22,190	13.84	NA		
Boceprevir+ PegIFN+RBV	31,832	14.28	9,642	0.44	Extended dominance
Telaprevir+ PegIFN+RBV	35,210	14.67	13,020	0.83	
3D±RBV [a]	40,348	15.29	18,159	1.46	12,453
Sofosbuvir+ PegIFN+RBV	45,516	14.80	5,168	-0.49	Dominated

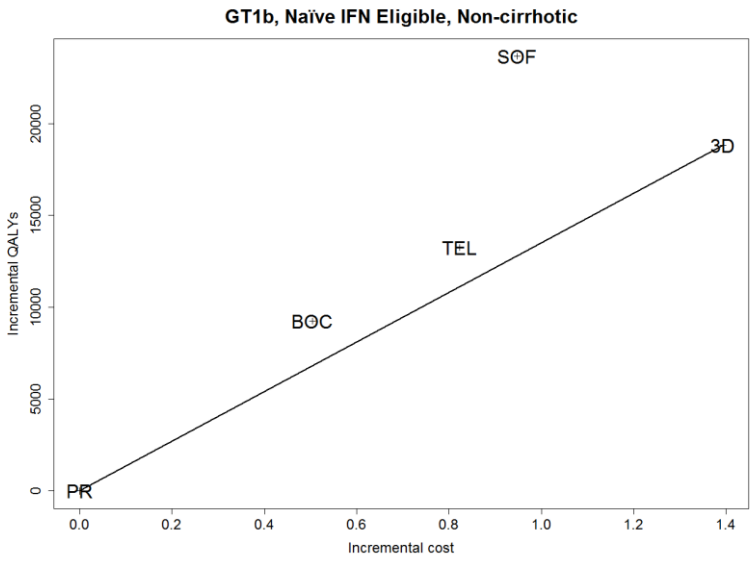


[a] Non-cirrhotic patients GT1b HCV are treated with 3D alone while all other GT1 patients receive 3D in combination with ribavirin

Table 6 GT1b, treatment-naive, IFN-eligible patients, by cirrhosis status

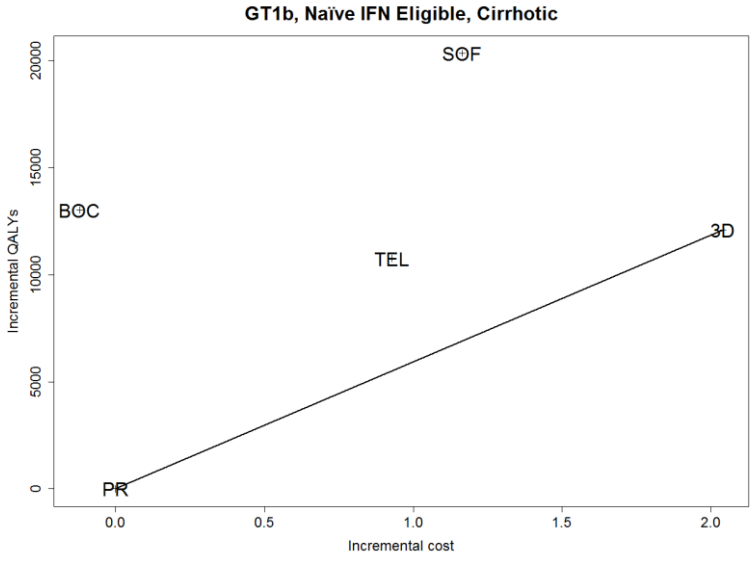
Genotype 1b, treatment-naive, interferon-eligible, non-cirrhotic

	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	19,844	14.45	NA		
Boceprevir+ PegIFN+RBV	29,110	14.95	9,265	0.50	Extended dominance
Telaprevir+ PegIFN+RBV	33,115	15.27	13,271	0.82	
3D	38,677	15.84	18,833	1.39	13,515
Sofosbuvir+ PegIFN+RBV	43,503	15.39	4,826	-0.45	Dominated



Genotype 1b, treatment-naive, interferon-eligible, cirrhotic

	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	43,298	8.32			
Telaprevir+ PegIFN+RBV	54,065	9.25	10,766	0.93	Extended dominance
3D+RBV	55,388	10.36	12,090	2.04	5,924
Boceprevir+ PegIFN+RBV	56,331	8.20	943	-2.16	Dominated
Sofosbuvir+ PegIFN+RBV	63,636	9.48	8,248	-0.88	Dominated



Section 2: Genotype 1, treatment-experienced, interferon-eligible patients

PegIFN+RBV and Telaprevir+PegIFN+RBV were the only comparators included in the company model for GT1 treatment-experienced, interferon-eligible patients. The cost effectiveness results for this population are similar to those for GT1 treatment-naive patients.

For the combined population of GT1a and GT1b (68.8% GT1a) patients, presented in the company base case, the ICER is less favourable for cirrhotic patients compared with non-cirrhotic patients (see Table 8). The incremental analysis for GT1 cirrhotic patients includes Telaprevir+PegIFN+RBV. This result is primarily due to the increased 3D+RBV treatment costs for GT1a patients with cirrhosis.

For treatment-experienced GT1a patients with cirrhosis incremental cost with 3D+RBV is approximately two and a half times the incremental cost for non-cirrhotic patients (see Table 10), reflecting the increased treatment duration for this group of patients. While the QALY gain for cirrhotic patients is also higher than for non-cirrhotic patients, it has not increased in proportion with the increased incremental cost, resulting in a less favourable ICER for cirrhotic patients compared with non-cirrhotic patients. In contrast, for GT1b patients the ICER for cirrhotic patients is more favourable than for non-cirrhotic patients (see Table 12).

Table 7 GT1, treatment-experienced, IFN-eligible patients, all fibrosis stages

Genotype 1 (68.8% GT1a), treatment-experienced, interferon-eligible, all stages of fibrosis (mild, moderate and compensated cirrhosis)					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	30,128	11.07	NA		
Telaprevir+ PegIFN+RBV	42,646	12.10	12,518	1.04	Extended dominance
3D±RBV	51,882	13.19	21,754	2.12	10,258

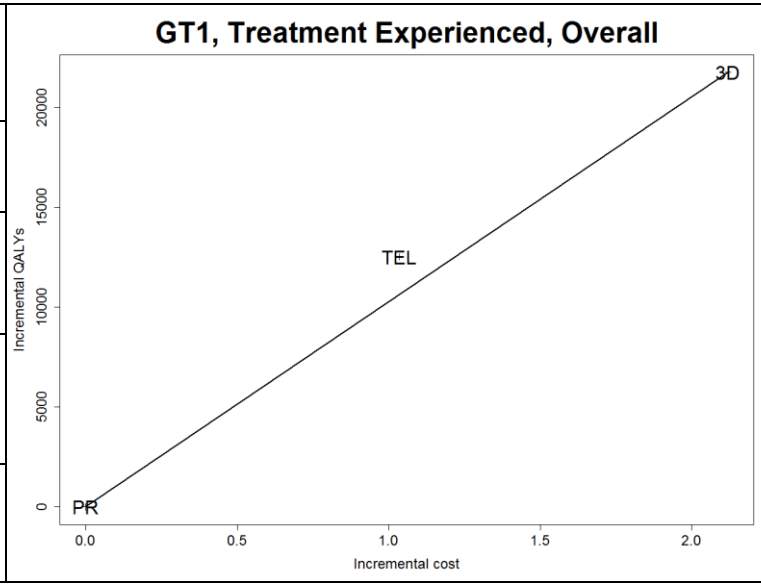
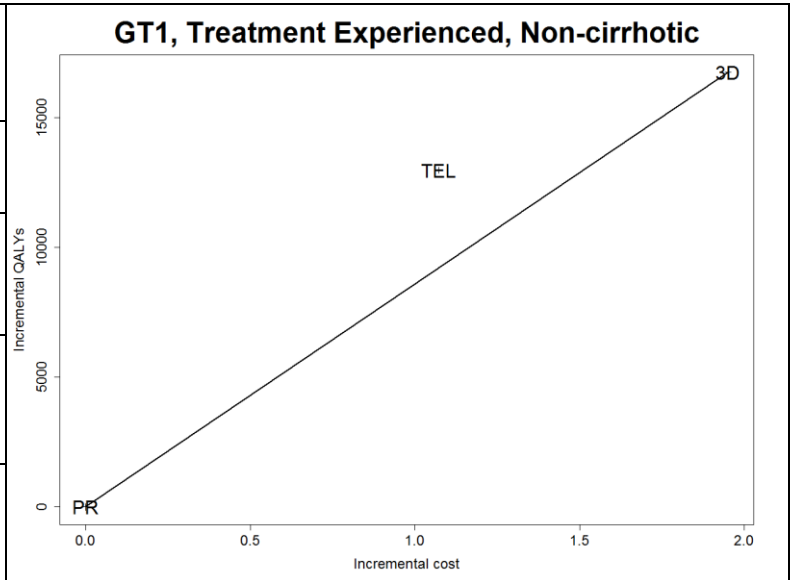


Table 8 GT1, treatment-experienced, IFN-eligible patients, by cirrhosis status

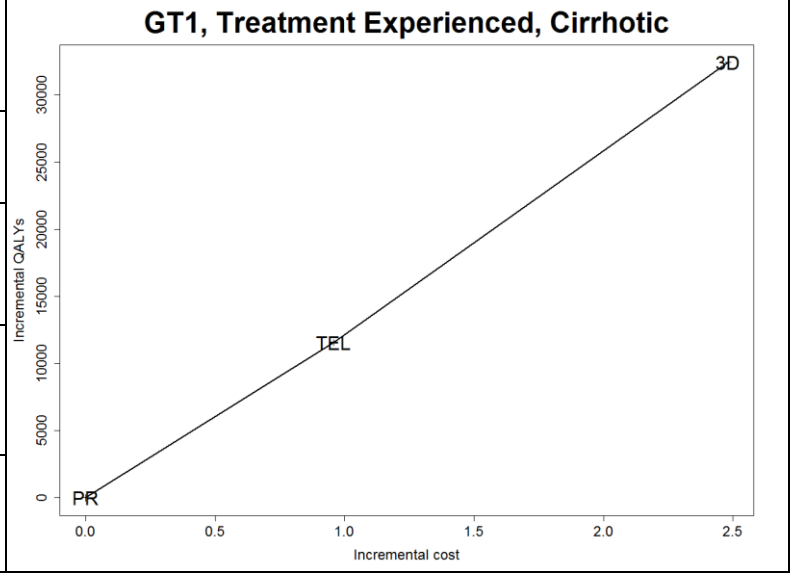
Genotype 1 (68.8% GT1a), treatment-experienced, interferon-eligible, non-cirrhotic

	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	22,432	12.82	NA		
Telaprevir+ PegIFN+RBV	35,402	13.90	12,970	1.07	Extended dominance
3D±RBV	39,173	14.78	16,741	1.95	8,581



Genotype 1 (68.8% GT1a), treatment-experienced, interferon-eligible cirrhotic

	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	46,482	7.33	NA		
Telaprevir+ PegIFN+RBV	58,040	8.29	11,557	0.96	12,071
3D+RBV	78,890	9.81	32,407	2.48	13,060



Genotype 1a, treatment-experienced, interferon-eligible patients

Table 9 GT1a, treatment-experienced, IFN-eligible patients, all fibrosis stages

Genotype 1a treatment-experienced, interferon-eligible, all stages of fibrosis (mild, moderate and compensated cirrhosis)					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	29,458	11.16	NA		
Telaprevir+ PegIFN+RBV	43,559	11.96	14,101	0.80	Extended dominance
3D+RBV	55,552	13.17	26,093	2.01	12,978

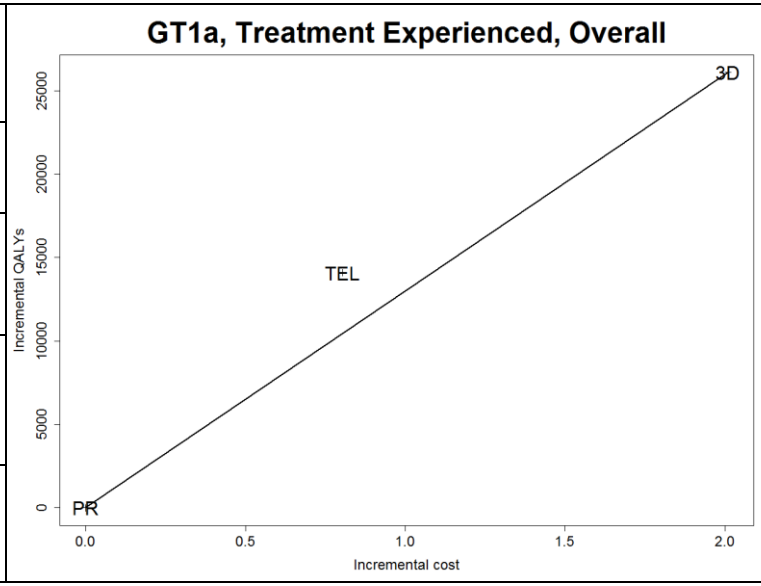
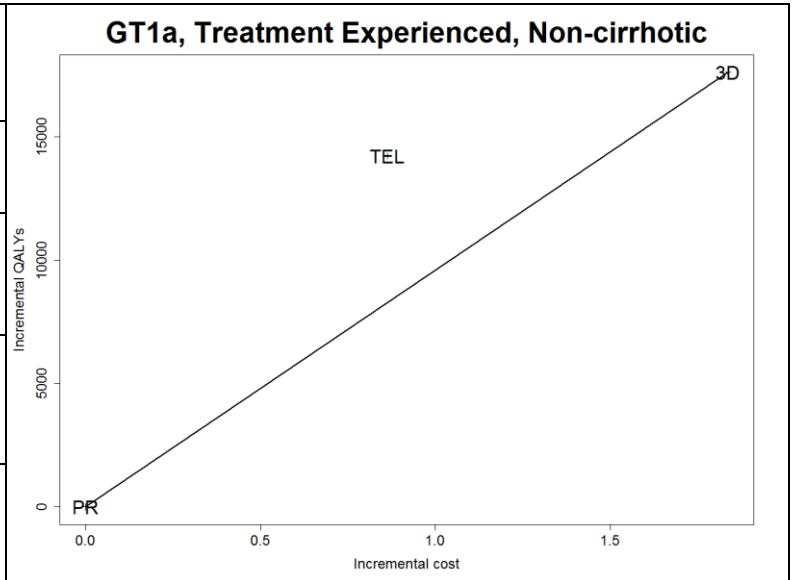


Table 10 GT1a, treatment-experienced, IFN-eligible patients, by cirrhosis status

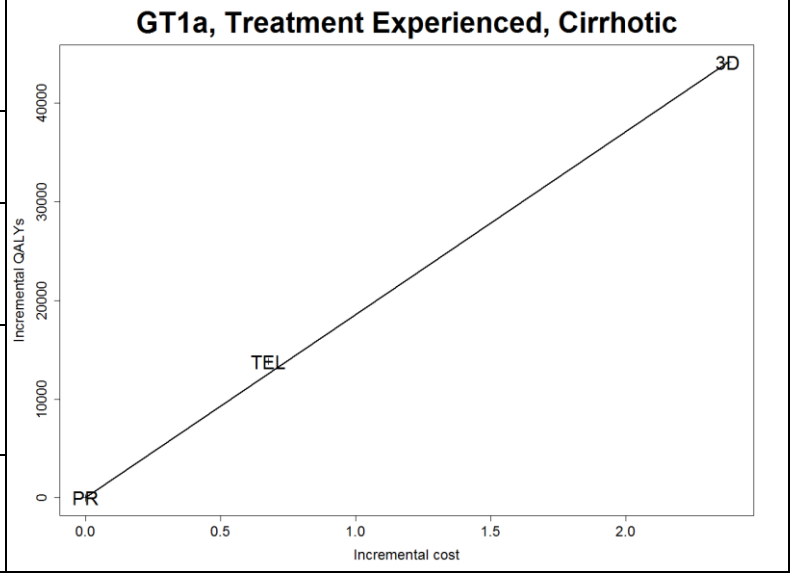
Genotype 1a treatment-experienced, interferon-eligible, non-cirrhotic

	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	21,907	12.91	NA		
Telaprevir+ PegIFN+RBV	36,138	13.77	14,231	0.86	Extended dominance
3D+RBV	39,524	14.74	17,617	1.84	9,589



Genotype 1a, treatment-experienced, interferon-eligible cirrhotic

	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	45,505	7.45	NA		
Telaprevir+ PegIFN+RBV	59,328	8.13	13,823	0.68	Extended dominance
3D+RBV	89,610	9.83	44,105	2.38	18,539



Genotype 1b, treatment-experienced, interferon-eligible patients

Table 11 GT1b, treatment-experienced, IFN-eligible patients, all fibrosis stages

Genotype 1b treatment-experienced, interferon-eligible, all stages of fibrosis (mild, moderate and compensated cirrhosis)					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	30,738	10.98	NA		
Telaprevir+ PegIFN+RBV	41,579	12.26	10,841	1.28	Extended dominance
3D±RBV	43,790	13.22	13,052	2.24	5,828

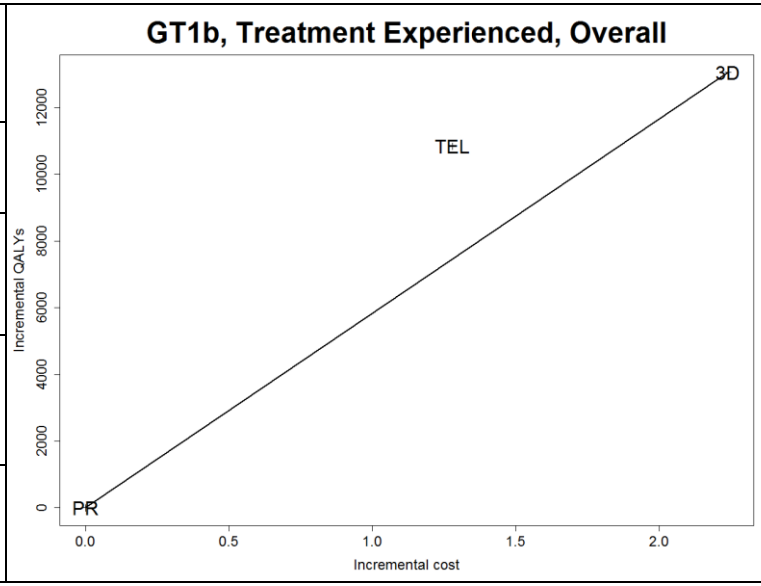
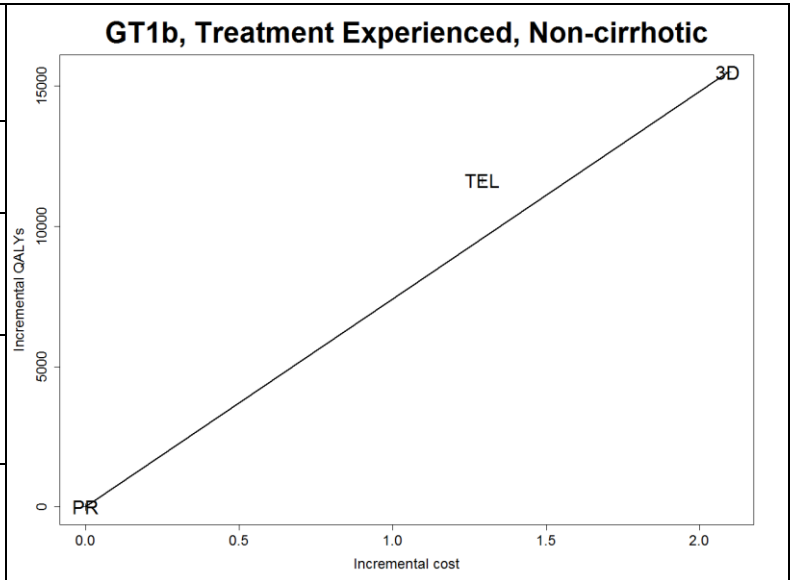


Table 12 GT1b, treatment-experienced, IFN-eligible patients, by cirrhosis status

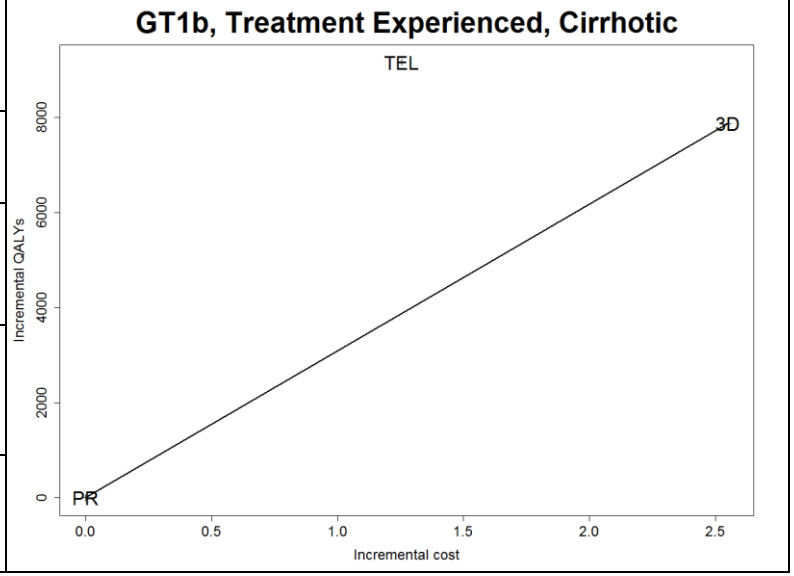
Genotype 1b, treatment-experienced, interferon-eligible, non-cirrhotic

	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	22,909	12.75	NA		
Telaprevir+ PegIFN+RBV	34,542	14.04	11,633	1.29	Extended dominance
3D	38,398	14.84	15,489	2.09	7,401



Genotype 1b, treatment-experienced, interferon-eligible cirrhotic

	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	47,375	7.22	NA		
Telaprevir+ PegIFN+RBV	56,534	8.47	9,159	1.25	Extended dominance
3D+RBV	55,249	9.77	7,874	2.55	3,087



Section 3: Genotype 4, interferon-eligible patients

Fewer comparators were included in the company model for GT4 patients. These were limited to PegIFN+RBV for treatment-naive patients (and sofosbuvir+PegIFN+RBV for non-cirrhotic treatment-naive patients) and best supportive care for other patient groups. The company submission only presented analyses for non-cirrhotic patients due to a lack of efficacy evidence for GT4 cirrhotic patients. We have included cost effectiveness estimates for GT4 cirrhotic patients using efficacy data for 24 weeks of treatment with 2D in GT1b HCV patients. These data were not reported in the CS but are discussed in the European Public Assessment Report (EPAR) for ombitasvir /paritaprevir /ritonavir, which noted a similarity of in vitro effect of 2D on GT1b and GT4 HCV (discussed in the NICE pre-meeting briefing for this appraisal). The SVR used for this population was 0.97 for both treatment-naive and treatment-experienced patients.

Table 13 reports the results from the company model for non-cirrhotic GT4 patients (also reported in the CS). Table 14 reports ICERs for cirrhotic GT4 patients treated with 2D+RBV. GT4 patients with cirrhosis are treated for 24 weeks with 2D+RBV which results in less favourable ICERs for this group of patients compared with non-cirrhotic GT4 patients, who are treated for 12 weeks.

Table 13 GT4, non-cirrhotic, IFN-eligible patients

Genotype 4 treatment-naive, interferon-eligible, non-cirrhotic patients					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV	19,286	15.00	NA		
2D+RBV (12 weeks)	36,490	15.84	17,204	0.85	20,351
Sofosbuvir+PegIFN+RBV	41,237	15.81	21,951	0.81	Dominated
Genotype 4 treatment-experienced, interferon-eligible, non-cirrhotic patients					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
Best supportive care[a]	16,186	12.58	NA		
2D+RBV (12 weeks)	36,536	14.84	20,350	2.27	8,977

[a] The model is set up to allow a comparison with best supportive care (termed “no treatment” in the model) which has an assumed SVR of zero.

Table 14 GT4, cirrhotic, IFN-eligible patients

Genotype 4 treatment-naive, interferon-eligible, cirrhotic patients					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
PegIFN+RBV[a]	40,613	9.01	NA		
Best supportive care[b]	42,809	7.23	2,196	-1.78	Dominated
2D+RBV (24 weeks)[c]	86,646	10.27	46,032	1.26	36,472
Genotype 4 treatment-experienced, interferon-eligible, cirrhotic patients					
	Total		Incremental		ICER (£ per QALY gained)
	Cost (£)	QALY	Cost (£)	QALY	
Best supportive care[b]	41,370	7.03	NA		
2D+RBV (24 weeks)[c]	85,502	9.82	44,132	2.78	15,868

[a] SVR for PegIFN+RBV in GT4 patients with cirrhosis in the model is 60% - no source is reported for this SVR. The ERG notes that the overall SVR for the study reported by Kamal and colleagues[1] was 59.9% and assumes this may be the source used. The study does not report SVR by stage of fibrosis, or for cirrhotic and non-cirrhotic patients separately. It is also not clear what proportion of patients in the study had developed cirrhosis – the study only reports the median and range of fibrosis scores (median = 1, range (0-4)).
[b] The model is set up to allow a comparison with best supportive care (termed "no treatment" in the model) which has an assumed SVR of zero.
[c] SVR for 2D+RBV (24 weeks) assumed to be 97% (reported for 2D 24 weeks for GT1b HCV) – based on similarity of in vitro effect of 2D on GT1b and GT4 HCV noted in the EPAR for ombitasvir /paritaprevir /ritonavir (referenced in the NICE pre-meeting briefing for this appraisal). The SVR for GT1b patients was estimated in a study including both treatment-naive and treatment-experienced patients (separate SVR by treatment experience was not reported in EPAR)

Reference List

(1) Kamal SM, Ahmed A, Mahmoud S, Nabegh L, El Gohary I, Osaban I et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4: A randomized trial and quality of life analysis. *Liver International* 2011; 31(3):401-411.