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

ERG commentary on company additional analyses

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Overview

Following the first Appraisal Committee meeting for the STA of ombitasvir/ paritaprevir/ ritonavir with or without dasabuvir for treating chronic hepatitis C, NICE requested the company to conduct additional analyses. The company's response includes a 72 page document (detailing the analyses undertaken, assumptions underlying the analyses and tabulations of their results) and an updated, executable version of the company model. The document detailing the company response contains relatively little narrative discussion of the results and has no overall summary of their findings. The document does not have page numbers, nor does it include tables of contents and figures (despite including 84 tables and 32 figures) which make it difficult to identify each section within the report. Because of this we will avoid making explicit reference to pages in the in the company response, but will direct our commentary toward the constituent sections of the response and to specific tables where necessary.

The company response follows the bullet points in the NICE specification of additional analyses and is structured under five broad headings and we have followed this framework in constructing this commentary:

1) Revised incremental cost-effectiveness analyses for the different regimens of ombitasvir/paritaprevir/ritonavir with or without dasabuvir (3D or 2D)
   - using regimens and durations specified in the summary of product characteristics
   - presented separately for people with and without cirrhosis, and by treatment history
   - including all NICE recommended comparators
2) Provide scenario analyses around utility values
   a) using the utility increment for SVR over the baseline utility values, based on values reported for people who achieved SVR in the trials
   b) using alternative health state utility values based on the EQ-5D data from the trials
3) Confirm the marketing position of AbbVie relating to 12 weeks' treatment in people with genotype 1a chronic hepatitis C with cirrhosis and provide justification for a 12 week treatment regimen in this population. Comment whether a 12 week treatment with 2D plus ribavirin would be an option for some patients with genotype 4 chronic hepatitis C with cirrhosis. Provide relevant details from the clinical guideline (published in March/April 2015) that has made recommendations relating to the use/duration of 3D plus ribavirin and 2D plus ribavirin for these populations.
4) Using appropriate SVR rates (for the 12 week regimen or 24 week regimen) from the TURQUOISE II trial, provide subgroup analyses to explore the effect on the incremental cost-effectiveness ratios (ICERs) of the following:

a) 12 week treatment duration of 3D plus ribavirin for people with treatment naïve genotype 1a CHC with compensated cirrhosis
b) 12 week treatment duration of 3D plus ribavirin for treatment experienced genotype 1a CHC with compensated cirrhosis who have relapsed after achieving SVR with previous therapy
c) 12 week treatment duration of 3D plus ribavirin for treatment experienced genotype 1a CHC with compensated cirrhosis who have achieved a partial response to previous therapy
d) 24 week treatment duration of 3D plus ribavirin for treatment experienced genotype 1a CHC with compensated cirrhosis who had not responded to previous therapy (null responders).

5) Provide probabilistic sensitivity analyses for each base-case analyses varying parameters to a meaningful degree around the value used in the base-case, with the source and rationale for each variation.

The document detailing the company response does not report input data used in the model (for example SVRs), but states that detailed descriptions of the data and sources are included in the electronic model. Since this information will not be available to the appraisal committee when considering these analyses, the ERG has extracted these data from the model and presents these at the end of this document (see Table 15 to Table 19). Other input data used in the additional analyses (such as utility data required for the scenario analyses in section 2) will be presented and discussed in the relevant sections of this commentary.

The ERG noted some errors in the tables presented in the company's additional analyses. These are reported at the end of this documented (see Appendix 1), with corrected values reported for the relevant tables

1. Revised incremental cost-effectiveness analyses for the different regimens of ombitasvir/paritaprevir/ritonavir with or without dasabuvir (3D or 2D)

Input data and assumptions for these analyses were identical to those included in the original company submission, except for the inclusion of Simeprevir+PegIFN+RBV (for both treatment-naïve and treatment-experienced patients) and Sofosbuvir+PegIFN+RBV (for treatment-experienced patients) as requested in the NICE specification.

Clinical effectiveness, adverse events and treatment duration with Simeprevir+PegIFN+RBV

The SVRs for Simeprevir+PegIFN+RBV, used in the analysis, were derived from simple pooling of the results reported for the intention-to-treat (ITT) population in the QUEST 1 and QUEST 2 trials of Simeprevir+PegIFN+RBV vs PegIFN+RBV. As noted in the company's response, the population included in the trials does not exactly correspond to the marketing authorisation for Simeprevir. However this is the only population where SVRs are reported by stage of fibrosis, as required for the model. Using data on outcomes for the ITT population is likely to underestimate the effectiveness of Simeprevir+PegIFN+RBV in GT1 patients, since Q80K polymorphism confers resistance to Simeprevir and is associated with lower SVR than in patients without this polymorphism. The company also notes that the definition of fibrosis stages reported in the QUEST publications does not match the definitions used in the economic model. This seems to be a less significant issue than the use of the ITT population, particularly given that SVR data for mild and moderate fibrosis have been combined for other treatment regimens in the model (see Table 15).

SVRs for GT1 treatment-experienced patients were based on data for the Simeprevir+ PegIFN+RBV arms in a range of trials (null responders and partial responders from the ATTAIN trial, and prior responders from the PROMISE trial). SVRs for GT4 patients (both treatment-naïve and treatment-experienced) were taken from the RESTORE trial.

The company response document doesn't discuss the duration of treatment or adverse events for treatment with Simeprevir+ PegIFN+RBV. Examination of the electronic model indicates that these are based on the Simeprevir+PegIFN+RBV arms in the same clinical trials that were used to derive the SVR estimates.

Clinical effectiveness, adverse events and treatment duration with Sofosbuvir+PegIFN+RBV

The company was not able to identify any suitable trial evidence on SVR for treatment-naïve GT4 patients with cirrhosis receiving Sofosbuvir+PegIFN+RBV. In order to include these patients in the analysis they assumed that the SVR for GT1 treatment-naïve cirrhotic patients

could be applied. The company response does not include any discussion on the clinical plausibility of this assumption.

In the absence of suitable trial evidence on SVR for any group of treatment-experienced patients the company have used values from the CS for sofosbuvir/ ledipasvir, but do not identify where that submission sourced these data or give any indication of their validity or reliability. The ERG has checked the submission (at https://www.nice.org.uk/guidance/gid-tag484/documents/hepatitis-c-chronic-ledipasvirsofosbuvir-id742-committee-papers) and note that the SVRs are for GT1 treatment-naïve patients and were derived from the NEUTRINO study and sourced to the sofosbuvir SPC. The company response does not include any discussion on the clinical plausibility of this assumption – in particular there is no discussion of the plausibility of the assumption of equal effectiveness across all categories of prior treatment response, given that all other PegIFN containing regimens show a lower response in null responders versus partial responders and prior relapsers.

The duration of treatment and adverse event data used in the model are also based on data from the Neutrino study and use the same assumption (that data for GT1 treatment-naïve patients can be applied to all other patient groups).

These analyses suffer from the same issues as those reported in the original CS, and noted in the ERG report. The economic analyses are all based on unadjusted indirect comparisons – the company response does not contain any discussion of the relative effectiveness of comparators compared with a common base, even where such a common base exists (PegIFN+RBV). While accepting that the design of the trials of ombitasvir/ paritaprevir/ ritonavir with or without dasabuvir limit the possibility of developing complete evidence networks to perform adjusted indirect comparisons, the ERG feels that the original CS and the company response could have given more consideration to the face validity of these comparisons, by reporting the relative effectiveness of each comparator versus PegIFN+RBV. The ERG suggests that the results of these analyses should be treated with caution, given the nature of the indirect comparisons in the model and the increasing range of assumption/ imputation used to populate the model.

The ERG have summarised the tables by removing dominated/ extendedly dominated comparators, to enable all comparisons for each GT / patient treatment history combination to fit on one page. The results in Table 1 for all patients (irrespective of the stage of fibrosis) are identical to the base case in the original CS and the results stratified by cirrhosis status are identical to the results of additional analysis undertaken by the ERG and presented at first ACM. Overall the ICERs for treatment with 3D and 2D are less favourable in cirrhotic patients, when treatment duration increases to 24 weeks and comparators that were excluded by extended dominance in other populations remain in the analysis.

Table 1: Genotype 1, treatment-naïve interferon eligible.

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Genotype 1					
Additional analysis Table 1: Any stage of fibrosis (Base Case Table 137 in original CS)					
PegIFN+RBV	22,872	13.72	NA	NA	NA
3D±RBV	43,624	15.21	20,752	1.5	13,864
Additional analysis Table 2: Non-cirrhotic					
PegIFN+RBV	20,483	14.33	NA	NA	NA
3D±RBV	39,556	15.77	19,073	1.43	13,306
Additional analysis Table 3: Cirrhotic					
PegIFN+RBV	44,374	8.18	NA	NA	NA
SOF+PegIFN+RBV	61,777	9.73	17,402	1.56	11,182
3D+RBV	80,238	10.24	35,864	2.07	36,139
Genotype 1a					
Additional analysis Table 4: Any stage of fibrosis (Table 143 in original CS)					
PegIFN+RBV	23,305	13.64	NA	NA	NA
3D+RBV	45,110	15.18	21,805	1.54	14,199
Additional analysis Table 5: Non-cirrhotic					
PegIFN+RBV	20,888	14.26	NA	NA	NA
3D+RBV	39,955	15.73	19,067	1.47	12,949
Additional analysis Table 6: Cirrhotic					
PegIFN+RBV	45,057	8.08	NA	NA	NA
SOF+PegIFN+RBV	61,347	9.79	16,290	1.7	9,555
3D+RBV	91,507	10.19	46,450	2.11	75,360
Genotype 1b					
Additional analysis Table 7: Any stage of fibrosis (Table 144 in original CS)					
PegIFN+RBV	22,190	13.84	NA	NA	NA
3D±RBV	40,348	15.29	18,159	1.46	12,453
Additional analysis Table 8: Non-cirrhotic					
PegIFN+RBV	19,844	14.45	NA	NA	NA
3D	38,677	15.84	18,833	1.39	13,515
Additional analysis Table 9: Cirrhotic					
PegIFN+RBV	43,298	8.32	NA	NA	NA
3D+RBV	55,388	10.36	12,090	2.04	5,924

Notes: the summary results of these analyses are identical to those submitted by the ERG prior to the first Appraisal Committee meeting, since simeprevir+pegIFN+RBV (comparator added to the analysis at the request of NICE is extendedly dominated in all the above analyses).

Table 2: Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Genotype 1					
Additional analysis Table 10: Any stage of fibrosis (Base Case Table 138 in original CS)					
PegIFN+RBV	30,128	11.07	NA	NA	NA
3D±RBV	51,882	13.19	21,754	2.12	10,258
Additional analysis Table 11: Non-cirrhotic					
PegIFN+RBV	22,432	12.82	NA	NA	NA
3D±RBV	39,173	14.78	16,741	1.95	8,581
Additional analysis Table 12: Cirrhotic					
PegIFN+RBV	46,482	7.33	NA	NA	NA
SOF+PegIFN+RBV	64,197	8.87	17,714	1.54	11,492
3D+RBV	78,890	9.81	32,407	2.48	15,631
Genotype 1a					
Additional analysis Table 13: Any stage of fibrosis (Table 145 in original CS)					
PegIFN+RBV	29,458	11.16	NA	NA	NA
3D+RBV	55,552	13.17	26,093	2.01	12,978
Additional analysis Table 14: Non-cirrhotic					
PegIFN+RBV	21,907	12.91	NA	NA	NA
3D+RBV	39,524	14.74	17,617	1.84	9,589
Additional analysis Table 15: Cirrhotic					
PegIFN+RBV	45,505	7.45	NA	NA	NA
SOF+PegIFN+RBV	64,197	8.87	18,692	1.42	13,157
3D+RBV	89,610	9.83	44,105	2.38	26,516
Genotype 1b					
Additional analysis Table 16: Any stage of fibrosis (Table 146 in original CS)					
PegIFN+RBV	30,738	10.98	NA	NA	NA
3D±RBV	43,790	13.22	13,052	2.24	5,828
Additional analysis Table 17: Non-cirrhotic					
PegIFN+RBV	22,909	12.75	NA	NA	NA
3D	38,398	14.84	15,489	2.09	7,401
Additional analysis Table 18: Cirrhotic					
PegIFN+RBV	47,375	7.22	NA	NA	NA
3D+RBV	55,249	9.77	7,874	2.55	3,087

Table 3: Genotype 4 treatment-naïve, interferon eligible

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Additional analysis Table 19: Any stage of fibrosis					
PegIFN+RBV	21,940	14.33	NA	NA	NA
2D+RBV	41,401	15.29	19,462	0.96	20,234
Additional analysis Table 20: Non-cirrhotic (Table 139 in original CS)					
PegIFN+RBV	19,286	15.00	NA	NA	NA
2D+RBV	36,490	15.84	17,204	0.85	20,351
Additional analysis Table 21: Cirrhotic					
PegIFN+RBV	45,822	8.32	NA	NA	NA
SMV+PegIFN+RBV	55,377	9.28	9,555	0.96	9,902
SOF+PegIFN+RBV	61,777	9.73	15,955	1.41	14,238
2D+RBV	85,602	10.33	39,781	2.01	40,025

Table 4: Genotype 4 treatment-experienced (overall), interferon eligible

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Additional analysis Table 22: Any stage of fibrosis					
No treatment	24,245	10.80	NA	NA	NA
2D+RBV	52,199	13.24	27,954	2.43	11,485
Additional analysis Table 23: Non-cirrhotic (Table 140 in original CS)					
No treatment	16,186	12.58	NA	NA	NA
2D+RBV	36,536	14.84	20,350	2.27	8,977
Additional analysis Table 24: Cirrhotic					
No treatment	41,370	7.03	NA	NA	NA
SOF+PegIFN+RBV	64,197	8.87	22,827	1.84	12,432
2D+RBV	85,482	9.82	44,112	2.79	22,331

2. Scenario analyses around utility values

The scenario analyses around utility values use the same input data as described above in section 1, hence use regimens and treatment duration for 3D and 2D as specified in the summary of product characteristics, include all relevant comparators and are presented separately for people with and without cirrhosis, and by treatment history.

2a) Using the utility increment for SVR over the baseline utility values, based on values reported for people who achieved SVR in the trials

The pooled analysis from the company clinical trials indicated a lower utility gain for patients achieving an SVR ([redacted] vs +0.05 in the base case). The ERG cannot verify this estimate since no further information is provided in the company response. The analysis is based on patients having an SVR and who had baseline and 12 week post-treatment EQ-5D-5L. Data on EQ-5D-5L index values in the original CS are only reported as mean values across all patients in each trial (at baseline, at end of treatment and at 12 weeks post-treatment) and are not reported separately for those achieving SVR. Table 5 shows the health state utilities for base case and those included in this scenario analysis.

Table 5: Health state utility values in model base case and scenario analyses

State	Base case	Scenario a)
Mild HCV	0.77	0.770
Moderate HCV	0.66	0.660
Compensated cirrhosis	0.55	0.550
Recovered (no HCV, history of mild fibrosis)	0.82	[redacted]
Recovered (no HCV, history of moderate fibrosis)	0.71	[redacted]
Recovered (no HCV, history of compensated cirrhosis)	0.60	[redacted]
Decompensated cirrhosis	0.45	0.450
Hepatocellular carcinoma	0.45	0.450
Liver transplant	0.45	0.450
Post-liver transplant	0.67	0.670

As would be anticipated, reducing the utility gain associated with SVR states results in higher ICERs than in the base case analyses reported in the original CS, and compared with the analyses reported in section 1 of the company response (which used the base case health state utilities).

Table 6: Genotype 1, treatment-naïve interferon eligible. Scenario 2a

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Genotype 1					
Additional analysis Table 25: Ant stage of fibrosis					
PegIFN+RBV	22,872	13.40	NA	NA	NA
3D±RBV	43,624	14.50	20,752	1.11	18,772
Additional analysis Table 26: Non-cirrhotic					
PegIFN+RBV	20,483	14.00	NA	NA	NA
3D±RBV	39,556	15.04	19,073	1.04	18,297
Additional analysis Table 27: Cirrhotic					
PegIFN+RBV	44,374	7.97	NA	NA	NA
SOF+PegIFN + RBV	61,777	9.23	17,402	1.26	13,815
3D+RBV	80,238	9.64	35,864[a]	1.67[a]	44,632
Genotype 1a					
Additional analysis Table 28: Any stage of fibrosis					
PegIFN+RBV	23,305	13.34	NA	NA	NA
3D+RBV	45,110	14.48	21,805	1.13	19,252
Additional analysis Table 29: Non-cirrhotic					
PegIFN+RBV	20,888	13.95	NA	NA	NA
3D+RBV	39,955	15.02	19,067	1.07	17,833
Additional analysis Table 30: Cirrhotic					
PegIFN+RBV	45,057	7.89	NA	NA	NA
SOF+PegIFN+RBV	61,347	9.27	16,290	1.38	11,816
3D+RBV	91,507	9.60	46,450[b]	1.70[b]	92,268
Genotype 1b					
Additional analysis Table 31: Any stage of fibrosis					
PegIFN+RBV	22,190	13.48	NA	NA	NA
3D±RBV	40,348	14.56	18,159	1.08	16,820
Additional analysis Table 32: Non-cirrhotic					
PegIFN+RBV	19,844	14.08	NA	NA	NA
3D	38,677	15.10	18,833	1.02	18,538
Additional analysis Table 33: Cirrhotic					
PegIFN+RBV	43,298	8.08	NA	NA	NA
3D+RBV	55,388	9.73	12,090	1.65	7,316

Notes
[a] calculated as increment vs PegIFN+RBV as baseline. Correctly calculated vs next best (non-dominated option) incremental cost = 18,461 and incremental QALYs = 0.41 giving ICER of 44,632 shown in final column.
[b] calculated as increment vs PegIFN+RBV as baseline. Correctly calculated vs next best (non-dominated option) incremental cost = 30,161 and incremental QALYs = 0.32 giving ICER of 92,828 shown in final column.

Table 7: Genotype 1, treatment-experienced (overall) interferon eligible. Scenario 2a

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Genotype 1					
Additional analysis Table 34: Any stage of fibrosis					
PegIFN+RBV	30,128	10.96	NA	NA	NA
3D±RBV	51,882	12.53	21,754	1.57	13,854
Additional analysis Table 35: Non-cirrhotic					
PegIFN+RBV	22,432	12.71	NA	NA	NA
3D±RBV	39,173	14.09	16,741	1.38	12,172
Additional analysis Table 36: Cirrhotic					
PegIFN+RBV	46,482	7.24	NA	NA	NA
SOF+PegIFN + RBV	64,197	8.48	17,714	1.24	14,331
3D+RBV	78,890	9.23	32,407	1.98	19,642
Genotype 1a					
Additional analysis Table 37: Any stage of fibrosis					
PegIFN+RBV	29,458	11.03	NA	NA	NA
3D+RBV	55,552	12.52	26,093	1.49	17,524
Additional analysis Table 38: Non-cirrhotic					
PegIFN + RBV	21,907	12.77	NA	NA	NA
3D+RBV	39,524	14.07	17,617	1.29	13,613
Additional analysis Table 39: Cirrhotic					
PegIFN +RBV	45,505	7.34	NA	NA	NA
SOF+PegIFN+RBV	64,197	8.48	18,692	1.14	16,387
3D+RBV	89,610	9.24	44,105	1.90	33,332
Genotype 1b					
Additional analysis Table 40: Any stage of fibrosis					
PegIFN+RBV	30,738	10.90	NA	NA	NA
3D±RBV	43,790	12.56	13,052	1.66	7,874
Additional analysis Table 41: Non-cirrhotic					
PegIFN+RBV	22,909	12.66	NA	NA	NA
3D	38,398	14.14	15,489	1.48	10,480
Additional analysis Table 42: Cirrhotic					
PegIFN + RBV	47,375	7.16	NA	NA	NA
3D+RBV	55,249	9.20	7,874	2.04	3,861

Table 8: Genotype 4 treatment-naïve, interferon eligible. Scenario 2a

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Additional analysis Table 43: Any stage of fibrosis					
PegIFN+RBV	21,940	13.83	NA	NA	NA
2D+RBV	41,401	14.56	19,462	0.73	26,730
Additional analysis Table 44: Non-cirrhotic					
PegIFN+RBV	19,286	14.47	NA	NA	NA
2D+RBV	36,490	15.10	17,204	0.63	27,422
Additional analysis Table 45: Cirrhotic					
PegIFN+RBV	45,822	8.08	NA	NA	NA
SMV+PegIFN+RBV	55,377	8.86	9,555	0.78	12,176
SOF+PegIFN+RBV	61,777	9.23	15,955	1.15	17,713
2D+RBV	85,602	9.71	39,781	1.63	48,791

Table 9: Genotype 4 treatment-experienced, interferon eligible. Scenario 2a

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Additional analysis Table 46: Any stage of fibrosis					
PegIFN+RBV	24,245	10.80	NA	NA	NA
2D+RBV	52,199	12.57	27,954	1.77	15,803
Additional analysis Table 47: Non-cirrhotic					
PegIFN+RBV	16,186	12.58	NA	NA	NA
2D+RBV	36,536	14.14	20,350	1.56	13,027
Additional analysis Table 48: Cirrhotic					
PegIFN+RBV	41,370	7.03	NA	NA	NA
SOF+PegIFN+RBV	64,197	8.48	22,827	1.44	15,800
2D+RBV	85,482	9.24	44,112	2.21	27,877

2b) Using health state utility values based on the EQ-5D data from the trials

The document detailing the company response provides no methodological detail on how these health state utility data were estimated. Examination of the electronic model ("Scenarios - Health Utilities" sheet) indicates that genotype- and fibrosis stage-specific estimates of the mean baseline utility were derived as weighted averages of the genotype and fibrosis stage-specific mean utilities derived for each trial. These values were used as the mild HCV, moderate HCV and compensated cirrhosis health state utilities.

Advanced liver disease states (decompensated cirrhosis, hepatocellular carcinoma, liver transplant) were not observed in the AbbVie trials, and as a result no utility data were collected for these health states in the trials. Utility values for these states were estimated based the ratio of the utility for each state, relative to mild HCV (in the utility value set used in the base case). For example, the ratio for decompensated cirrhosis using the values used in the base case is 0.45/0.77 (0.584) which can be multiplied by the genotype-specific utility for Mild HCV estimated in the trials (e.g. 0.850 for GT1 treatment-naïve patients) to derive an estimated health state utility for decompensated cirrhosis (0.584*0.850 = 0.497).

Values for SVR states were not based on the sub-group of patients achieving SVR but were based on a pooled estimate of the difference from baseline to 12 weeks post-treatment. The differences between mild HCV, moderate HCV and compensated cirrhosis and their respective SVR states in this analysis are greater (in absolute value, although some differences are positive and some negative with a range from -0.017 to +0.078) than those in the previous scenario which derived a single pooled value for the utility difference between chronic HCV infected and SVR states (in patients achieving SVR).

Table 10: Health state utility values in model base case and scenario analyses

State	Base case	GT1		GT4	
		Naive	Exper-ienced	Naive	Exper-ienced
Mild HCV	0.77	[redacted]	[redacted]	[redacted]	[redacted]
Moderate HCV	0.66	[redacted]	[redacted]	[redacted]	[redacted]
Compensated cirrhosis	0.55	[redacted]	[redacted]	[redacted]	[redacted]
Recovered (no HCV, history of mild fibrosis)	0.82	[redacted]	[redacted]	[redacted]	[redacted]
Recovered (no HCV, history of moderate fibrosis)	0.71	[redacted]	[redacted]	[redacted]	[redacted]
Recovered (no HCV, history of compensated cirrhosis)	0.60	[redacted]	[redacted]	[redacted]	[redacted]
Decompensated cirrhosis	0.45	[redacted]	[redacted]	[redacted]	[redacted]
Hepatocellular carcinoma	0.45	[redacted]	[redacted]	[redacted]	[redacted]
Liver transplant	0.45	[redacted]	[redacted]	[redacted]	[redacted]
Post-liver transplant	0.67	[redacted]	[redacted]	[redacted]	[redacted]

Notes: advanced liver disease states (decompensated cirrhosis, hepatocellular carcinoma, liver transplant) not observed in AbbVie trials. Utility for these states was estimated based the ratio of the utility for each state, relative to mild HCV. For example, the ratio for decompensated cirrhosis = 0.45/0.77 = 0.584 which when applied to the utility for Mild HCV in GT1 treatment-naïve patients ([redacted]) gives an estimated utility of 0.584*[redacted] = [redacted]

Table 11: Genotype 1, treatment-naïve interferon eligible. Scenario 2b

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Genotype 1					
Additional analysis Table 49: Any stage of fibrosis					
PegIFN+RBV	22,872	16.29	NA	NA	NA
3D±RBV	43,624	17.52	20,752	1.23	16,875
Additional analysis Table 50: Non-cirrhotic					
PegIFN+RBV	20,483	16.86	NA	NA	NA
3D±RBV	39,556	17.96	19,073	1.10	17,385
Additional analysis Table 51: Cirrhotic					
PegIFN+RBV	44,374	11.13	NA	NA	NA
SOF+PegIFN+RBV	61,777	12.95	17,402	1.83	9,535
3D+RBV	80,238	13.55	35,864	2.42	30,823
Genotype 1a					
Additional analysis Table 52: Any stage of fibrosis					
PegIFN+RBV	23,305	16.05	NA	NA	NA
3D+RBV	45,110	17.30	21,805	1.25	17,449
Additional analysis Table 53: Non-cirrhotic					
PegIFN+RBV	20,888	16.63	NA	NA	NA
3D+RBV	39,955	17.75	19,067	1.12	17,028
Additional analysis Table 54: Cirrhotic					
PegIFN+RBV	45,057	10.80	NA	NA	NA
SOF+PegIFN+RBV	61,347	12.76	16,290	1.96	8,312
3D+RBV	91,507	13.22	46,450	2.42	65,696
Genotype 1b					
Additional analysis Table 55: Any stage of fibrosis					
PegIFN+RBV	22,190	16.78	NA	NA	NA
3D±RBV	40,348	18.00	18,159	1.22	14,856
Additional analysis Table 56: Non-cirrhotic					
PegIFN+RBV	19,844	17.33	NA	NA	NA
3D	38,677	18.41	18,833	1.08	17,431
Additional analysis Table 57: Cirrhotic					
PegIFN+RBV	43,298	11.79	NA	NA	NA
3D+RBV	55,388	14.29	12,090	2.50	4,837

Table 12: Genotype 1, treatment-experienced (overall) interferon eligible. Scenario 2b

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Genotype 1					
Additional analysis Table 58: Any stage of fibrosis					
PegIFN+RBV	30,128	13.44	NA	NA	NA
3D±RBV	51,882	15.11	21,754	1.66	13,076
Additional analysis Table 59: Non-cirrhotic					
PegIFN+RBV	22,432	15.03	NA	NA	NA
3D±RBV	39,173	16.11	16,741	1.08	15,495
Additional analysis Table 60: Cirrhotic					
PegIFN+RBV	46,482	10.06	NA	NA	NA
SOF+PegIFN+RBV	64,197	11.86	17,714	1.80	9,840
3D+RBV	78,890	12.96	32,407	2.90	13,324
Genotype 1a					
Additional analysis Table 61: Any stage of fibrosis					
PegIFN + RBV	29,458	13.41	NA	NA	NA
3D+RBV	55,552	14.97	26,093	1.57	16,651
Additional analysis Table 62: Non-cirrhotic					
PegIFN + RBV	21,907	14.99	NA	NA	NA
3D+RBV	39,524	16.02	17,617	1.03	17,047
Additional analysis Table 63: Cirrhotic					
PegIFN+RBV	45,505	10.04	NA	NA	NA
SOF+PegIFN+RBV	64,197	11.65	18,692	1.61	11,610
3D+RBV	89,610	12.74	44,105	2.70	23,296
Genotype 1b					
Additional analysis Table 64: Any stage of fibrosis					
PegIFN+RBV	30,738	13.62	NA	NA	NA
3D±RBV	43,790	15.40	13,052	1.78	7,338
Additional analysis Table 65: Non-cirrhotic					
PegIFN+RBV	22,909	15.19	NA	NA	NA
3D	38,398	16.31	15,489	1.12	13,831
Additional analysis Table 66: Cirrhotic					
PegIFN+RBV	47,375	10.27	NA	NA	NA
3D+RBV	55,249	13.45	7,874	3.18	2,477

Table 13: Genotype 4 treatment-naïve, interferon eligible. Scenario 2b

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Additional analysis Table 67: Any stage of fibrosis					
PegIFN+RBV	21,940	16.85	NA	NA	NA
2D+RBV	41,401	17.89	19,462	1.04	18,783
Additional analysis Table 68: Non-cirrhotic					
PegIFN+RBV	19,286	17.54	NA	NA	NA
2D+RBV	36,490	18.47	17,204	0.92	18,673
Additional analysis Table 69: Cirrhotic					
PegIFN+RBV	45,822	10.59	NA	NA	NA
SMV+PegIFN+RBV	55,377	11.59	9,555	0.99	9,616
SOF+ PegIFN+RBV	61,777	12.05	15,955	1.46	13,806
2D+RBV	85,602	12.66	39,781	2.07	38,911

Table 14: Genotype 4 treatment-experienced, interferon eligible. Scenario 2b

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Additional analysis Table 70: Any stage of fibrosis					
PegIFN+RBV	24,245	13.50	NA	NA	NA
2D+RBV	52,199	16.32	27,954	2.81	9,935
Additional analysis Table 71: Non-cirrhotic					
PegIFN+RBV	16,186	15.26	NA	NA	NA
2D+RBV	36,536	17.69	20,350	2.43	8,370
Additional analysis Table 72: Cirrhotic					
PegIFN+RBV	41,370	9.77	NA	NA	NA
SOF+PegIFN+RBV	64,197	12.17	22,827	2.40	9,511
2D+RBV	85,482	13.40	44,112	3.63	17,355

3. Discussion of treatment duration (3D plus ribavirin) in people with genotype 1a chronic hepatitis C with cirrhosis.

The company response confirms that the marketing position allows for 12 weeks treatment with 3D for GT1a cirrhotic patients with baseline laboratory values of AFP < 20 ng/mL, platelets ≥ 90 x 109/L and albumin ≥ 35 g/L and that this is consistent with the summary of product characteristics. The response further cites efficacy data (SVR) from the TURQUOISE 2 study that indicates similar outcome for patients with compensated cirrhosis receiving either 12 or 24 weeks of treatment with 3D+RBV – with the exception of GT1a patients who were null responders to previous PegIFN+RBV treatment. The company response indicates that the original submission for marketing authorization to EMA proposed 12 weeks treatment for all GT1a cirrhotic patients (other than prior null responders who would receive 24 weeks treatment) and cites recommendations from a consensus meeting involving national societies (BASL, BHIVA, BIA, BSG, BVHG) indicating similar recommendations for GT1 patients treated with ombitasvir/paritaprevir/ritonavir with or without dasabuvir (±RBV). However the company response also states that (as noted above) the summary of product characteristics indicates that the recommendation for 12 weeks treatment in GT1a cirrhotic patients is based on baseline laboratory test results rather than prior treatment experience. It is not clear, from the submitted evidence, which approach would be used in practice – the ERG has not been able to verify these considerations with clinical experts.

The company response states that there is no recommendation to offer 12 weeks treatment to GT4 cirrhotic patients, who should receive 24 weeks of 2D+RBV.

4. Subgroup analyses to explore the effect on the incremental cost-effectiveness ratios (ICERs) of the treatment duration of 3D plus ribavirin for people with genotype 1a CHC with compensated cirrhosis

This section to follow

5. Provide probabilistic sensitivity analyses for each base-case analyses varying parameters to a meaningful degree around the value used in the base-case, with the source and rationale for each variation.

The presentation of the probabilistic evaluations for each base case analysis (including details of variation in parameter values, source and rationale for each variation) specified in the NICE request for additional analysis is limited to presentation of charts showing multiple CEACs. No summary values (such as mean costs and QALYs for each PSA with percentile-based confidence limits) are presented for comparison with the deterministic base case results, nor does the document report the required sources or rationales for variation around parameter values (other than for SVRs, providing some explanation and examples to supplement information provided in the original CS).

The PSAs reported in section 5 of the company response include evaluations in populations that do not appear to be relevant to the request for additional analyses from NICE (Figures 25-32 report analyses for interferon-ineligible patients that are not included in any of the deterministic analyses described in section 1 to 4 of the company response). In contrast the PSA section does not appear to include any analyses relating to the SVR and health state utility scenarios considered in section 2 or the treatment duration scenarios in section 4. While the wording of the NICE request is not explicit in stating which analysis should be included in the PSA, the company response does not include any rationale for limiting the PSA only to analyses specified in section 1.

The updated electronic model does not appear to have been amended in light of comments raised in the original ERG report regarding the approach to sampling variables in the PSA, nor have the additional analyses considered uncertainties related to assumptions underlying the analysis (for example additional uncertainty introduced by applying SVR data derived in studies of GT1 patients to GT4 patients). The company response refers to the use of “hypothetical numbers for sofosbuvir+PR” but uses these to derive a standard error to parameterise the sampling distribution in the PSA. For all SVRs, the variability in the PSA appears to be entirely based on statistical measures (standard errors) and does not consider any additional uncertainty introduced through the various assumptions and imputations that have been used to derive data to populate the model. The PSAs presented are therefore likely to underestimate the degree of uncertainty in the model.

Table 15: Treatment-naïve, interferon-eligible. SVR used in the model by genotype (genotype sub-group where relevant) and stage of fibrosis

Treatment regimen	Genotype sub-group											
	GT1			GT1a			GT1b			GT4		
	Fibrosis stage											
	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic
3D/ 2D	97.2		96.3	96.0 405/422		94.6 53/56	100.0 209/209		100.0 22/22	100.0 42/42		97.9 46/47
Simeprevir + PegIFN + RBV	83.9 317/378	73.2 60/82	60.4 29/48	79.1	68.4	55.7	89.3	78.6	65.9	84.4 27/32		66.7 2/3
Sofosbuvir + PegIFN + RBV	91.7 220/240		80.8 42/52	93.5		82.6	83.8		72.9	100.0 27/27		80.8 *
Telaprevir + PegIFN + RBV	81.3 109/134	71.6 149/208	61.9 13/21	78.0	68.3	58.6	85.9	76.2	66.4	NA	NA	NA
Boceprevir + PegIFN + RBV	65.9 220/337		31.3 5/16	60.8		26.2	68.0		33.4	NA	NA	NA
PegIFN + RBV	45.6 67/147	43.5 84/193	33.3 7/21	42.7	4.06	30.4	50.2	48.1	37.9	70.6 77/109		37.9 229/605

Notes:
* GT4 cirrhotic SVR is value for GT1

Table 16: Treatment-experienced (null responder), interferon-eligible. SVR used in the model by genotype (genotype sub-group where relevant) and stage of fibrosis

Treatment regimen	Genotype sub-group											
	GT1			GT1a			GT1b			GT4		
	Fibrosis stage											
	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic
3D/ 2D	96.8		95.1	95.4 83/87		92.9 39/42	100.0 32/32		100.0 25/25	100.0 23/23		96.0 24/25
Simeprevir+ PegIFN+ RBV	50.3 87/173		24.6 15/61	38.1		12.4	60.2		34.5	44.4 12/27		30.8 4/13
Sofosbuvir+ PegIFN+ RBV	74.0 178/240		65.2 34/52	74.0		65.2	74.0		65.2	74.0		65.2
Telaprevir+ PegIFN+ RBV	10.0 1/10	41.7 15/36	19.2 5/26	5.3	36.9	14.5	17.9	49.5	27.1	NA		
Boceprevir+ PegIFN+ RBV	NA											
PegIFN+ RBV	0.0 0/5	4.5 1/22	10 1/10	0.0	4.9	10.9	0.0	4.2	9.3	NA		

Table 17: Treatment-experienced (partial responder), interferon-eligible. SVR used in the model by genotype (genotype sub-group where relevant) and stage of fibrosis

Treatment regimen	Genotype sub-group											
	GT1			GT1a			GT1b			GT4		
	Fibrosis stage											
	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic
3D/ 2D	96.8		95.1	100.0 36/36		100.0 10/10	100.0 26/26		85.7 6/7	100.0 9/9		93.3 14/15
Simeprevir + PegIFN + RBV	72.9 86/118		55.6 15/27	59.2		41.8	82.3		65.0	100.0 5/5		20.0 1/5
Sofosbuvir + PegIFN + RBV	74.0 178/240		65.2 34/52	74.0		65.2	74.0		65.2	74.0		65.2
Telaprevir + PegIFN + RBV	71.4 5/7	75.0 18/24	33.3 6/18	62.2	65.8	24.1	80.4	84.0	42.3	NA		
Boceprevir + PegIFN + RBV	45.9	39.3	14.6	NA						NA		
PegIFN + RBV	0.0 0/10	25 3/12	20 1/5	0.0	31.6	25.3	0.0	16.9	13.5	NA		

Table 18: Treatment-experienced (prior relapser), interferon-eligible. SVR used in the model by genotype (genotype sub-group where relevant) and stage of fibrosis

Treatment regimen	Genotype sub-group											
	GT1			GT1a			GT1b			GT4		
	Fibrosis stage											
	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic
3D/ 2D	96.8		95.1	94.0 47/50		100.0 13/13	100.0 33/33		100.0 14/14	100.0 17/17		100.0 12/12
Simeprevir + PegIFN + RBV	82.0 137/167	72.7 32/44	74.4 29/39	73.1	63.8	65.4	88.7	79.4	81.1	91.7 11/12		80.0 8/10
Sofosbuvir + PegIFN + RBV	74.0 178/240		65.2 34/52	74.0		65.2	74.0		65.2	74.0		65.2
Telaprevir + PegIFN + RBV	85.3 29/34	83.1 69/83	82.1 23/28	81.8	79.7	78.7	88.9	86.7	85.7	NA		
Boceprevir + PegIFN + RBV	74.2	67.5	42.8	NA						NA		
PegIFN + RBV	35.0 7/20	21.2 7/33	2/15 13.3	40.9	27.1	19.2	30.8	17.0	9.2	NA		

Table 19: Treatment-experienced (overall), interferon-eligible. SVR used in the model by genotype (genotype sub-group where relevant) and stage of fibrosis

Treatment regimen	Genotype sub-group											
	GT1			GT1a			GT1b			GT4		
	Fibrosis stage											
	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic	Mild	Moderate	Cirrhotic
3D/ 2D	97.4		97.2	96.2		97.9	100.0		95.7	100.0		96.8
Simeprevir + PegIFN + RBV	69.8	66.0	53.8	58.4	54.7	42.5	78.2	74.5	62.3	80.0		472
Sofosbuvir + PegIFN + RBV	74.0		65.2	74.0		65.2	74.0		65.2	74.0		65.2
Telaprevir + PegIFN + RBV	58.5	68.3	48.6	53.0	62.7	43.1	65.0	74.7	55.1	NA		
Boceprevir + PegIFN + RBV	NA											
PegIFN + RBV	14.0	17.3	14.3	16.4	21.8	18.5	12.3	13.1	10.5	NA		

Appendix 1: Corrections to tables in company responses

Table 7: Genotype 1b treatment-naïve interferon eligible patients - Any Fibrosis Stage (repeats Table 4 i.e. gives data for genotype 1a). correct table in electronic model (on "Basecase - Incremental Analysis" sheet)– see below:

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. baseline	ICER incremental
Peg + Riba (PR)	£22,190	19.76	13.84	NA	NA	NA	NA	NA
PR + Boceprevir	£31,832	19.98	14.28	£9,642	0.22	0.44	£21,855	Extended dominance
PR + Telaprevir	£35,210	20.23	14.67	£13,020	0.48	0.83	£15,627	Extended dominance
Simeprevir + PR	£36,119	20.26	14.76	£13,929	0.51	0.92	£15,060	Extended dominance
AbbVie regimen	£40,348	20.64	15.29	£18,159	0.88	1.46	£12,453	£12,453
Sofosbuvir + PR	£45,516	20.33	14.80	£23,327	0.57	0.97	£24,084	Dominated

Table 27: Genotype 1 treatment-naïve interferon eligible patients – Cirrhotic Only Stage (repeats Table 26 i.e. gives data for non-Cirrhotic). Is incorrect in electronic model as well (on "SA - Pooled Increment on SVR" sheet). These data have been calculated by the ERG

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. baseline	ICER incremental
Peg + Riba (PR)	44,374		7.97	NA		NA	NA	NA
PR + Boceprevir	56,827		7.94	12,453		-0.03	-415,713	Dominated
PR + Telaprevir	55,132		8.72	10,757		0.75	14,306	Extended dominance
Simeprevir + PR	56,721		8.71	12,346		0.74	16,624	Extended dominance
Sofosbuvir + PR	61,777		9.23	17,402		1.26	13,815	13,815
AbbVie regimen	80,238		9.64	35,864*		1.67*	21,433	44,632

* calculated as increment vs PegIFN+RBV as baseline. Correctly calculated vs next best (non-dominated option) incremental cost = 18,461 and incremental QALYs = 0.41 giving ICER of 44,632 shown in final column.