NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Ombitasvir/paritaprevir/ritonavir with or without dasabuvir 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.

Table 1 Summary table of clinical and cost effectiveness for ombitasvir/paritaprevir/ritonavir with or without dasabuvir

SPC recommended regimens			Clinical evidence				Cost-effectiveness*	
Patient population	**Treatment**	**Duration weeks**	**Treatment history**	**Trial name**	**Trial arm/ subgroup meeting license**	**% achieving sustained virologic response at 12 week follow up; SVR12 (95% CI)**	**Company's ICER (£/QALY)*** not stratified for non-cirrhotic and cirrhotic patients	**ERG's exploratory ICER (£/QALY)** stratified for non-cirrhotic and cirrhotic patients
GT1b, without cirrhosis	3D	12	Naive	PEARL III	Treatment arm with 3D, n=91	100.0 (98.2-100.0)	12,453	13,515
			Experienced	PEARL II	Treatment arm with 3D, n = 209	100 (95.9-100.0)	5,828	7,401
GT1b, with compensated cirrhosis	3D+R	12	Naive	TURQUOISE II	Subgroup with GT1b in the 12 weeks treatment arm , n=68/208	98.5 (95.7-100.0)	12,453	5,924
			Experienced				5,828	3,087
GT1a, without cirrhosis	3D+R	12	Naive	SAPPHIRE I	Subgroup with GT1a, n=322/473	95.7 (93.4-97.9)	14,199	12,949
				PEARL IV	Treatment arm with 3D+RBV, n=100	97.0 (93.7-100.0)		

			Experienced	SAPPHIRE II	Subgroup with GT1a, n=173/297	96.0 (93.0-98.9)	12,978	9,589
GT1a, with compensated cirrhosis	3D+R	24	Naïve	TURQUOISE II	Subgroup with GT1a in the 24 weeks treatment arm, n=121/172	95.0 (91.2-98.9)	14,199	75,360
			Experienced				12,978	18,539
GT4 without cirrhosis	2D + R	12	Naïve	PEARL I	Treatment arms with 2D+RBV, Naive n=42,	100 (91.6-100)	20,351	20,351
			Experienced	PEARL I	Treatment arms with 2D+RBV, Experienced n=49,	100 (87.4-99.9)	8,977	8,977
GT4 with cirrhosis**	2D + R	24	Naïve	No trial data	Efficacy of 2D+R for 24 weeks for GT1b with cirrhosis from group 7 and 8 of PEARL , was used in the ERG's analysis	Not available for GT4** 97% for GT1b	Not reported	36,472
			Experienced					15,868

* The company did not present the ICERs for different regimens (with or without ribavirin and for different duration [12 weeks or 24]) in the specific patient populations based on subtypes of GT1 (1a and 1b) and presence of cirrhosis as defined in the SPC. In the base-case analyses the company presented ICERs for 4 different patient populations based on the genotype (GT1 or GT4) and treatment history (treatment naïve or treatment experienced). The ICERs for patients with subtypes 1a and 1b are taken from subgroup analyses (table 143 to146 of the company's submission, page 439-440). These ICERs were not stratified for non-cirrhotic and cirrhotic patient and were based on an assumption that 10% of treatment naïve and 32% of treatment experienced patients would have compensated cirrhosis at baseline.

The ERG calculated the ICERs for different regimens for different patient population groups as stipulated in the SPC please see tables 4, 6 and 8 of the addendum to the ERG report.

** The ERG conducted an exploratory analysis using effectiveness data of 2D regimen in patients with GT1b CHC with cirrhosis from PEARL I trial.

Key issues for consideration

Clinical practice

- The summary of product characteristics recommends different 3D regimens (in terms of concomitant administration of ribavirin and duration of treatment) for subtypes (1a and 1b) of GT1 CHC as follows;
  - People with GT1b without cirrhosis: 3D for 12 weeks.
  - People with GT1b with compensated cirrhosis: 3D+R for 12 weeks.
  - People with GT1a without cirrhosis: 3D+R for 12 weeks.
  - People with GT1a with compensated cirrhosis: 3D+R for 24 weeks.
  - If subtype is not known or in the case of CHC with mixed genotype 1 infection, it recommends following the treatment stipulated for subtype 1a.

  How does this relate to clinical practice; are these subtypes clearly defined and readily identifiable?

Decision problem

- The company excluded simeprevir as a comparator from its decision problem stating a lack of relevant clinical effectiveness data for this comparison. The ERG commented that using data from a publically available network meta-analysis, a comparison with simeprevir was possible. Given that simeprevir in combination with peginterferon alfa and ribavirin has been recommended for patients with GT1 and GT4 CHC in NICE technology guidance 331, is it appropriate for the company to exclude simeprevir from its decision problem?

Clinical effectiveness

- The ERG stated that the results from the completed trials of 3D and 2D included in the company's submission, may be subject to bias because:
  - Although the data were collected within randomised trials, the data relevant to the licensed indications were essentially observational data from individual trial arms and subgroup analyses.
  - For the trials evaluating 3D regimens in people with GT1CHC, the company compared the results with the results from historical trials evaluating telaprevir.

The ERG noted that there were higher proportions of patients with mild fibrosis in the 3D trials than the telaprevir trials, which may have biased the results in favour of 3D.

- No historical comparison was reported for the trial evaluating 2D regimen in people with GT4 CHC.
  However, the company also provided results from 2 ongoing trials (MALACHITE I and MALACHITE II) which directly compared 3D with telaprevir in people with GT1 CHC. The SVR12 data from these trials supported the findings from the completed trials. Can the results for sustained virological response 12 weeks after the end of treatment (SVR12) for the 3D and 2D regimens reported in the completed trials be considered robust?

- The ERG commented that some of the evidence for the treatment regimens were based on subgroup analyses from the trials (for example SAPPHIRE I and SAPPHIRE I) and it unlikely to be powered to demonstrate non-inferiority and superiority over historical control (telaprevir). Can these data be considered robust?
- The 24 week 2D+R regimen was not studied in clinical trials for people with GT4 CHC with compensated cirrhosis, but it is recommended in the summary of product characteristics for this patient population on the basis that it is effective in GT1b with cirrhosis and by extrapolation also in GT4 with cirrhosis. Is the evidence underpinning GT1b with cirrhosis from 1 phase II trial (PEARL I) suitable to inform efficacy for GT4 CHC with cirrhosis?
- The 3D and 2D regimens do not contain peginterferon alfa and therefore could be given to people who are intolerant to or ineligible for interferon treatment. The company did not present clinical effectiveness data specifically for this particular patient group. Can the 3D and 2D regimens be considered equally effective for people for whom peginterferon is considered appropriate and those who are intolerant to or ineligible for peginterferon? Can recommendations be made for people who are intolerant to or ineligible for peginterferon?
- The completed trials that established the clinical effectiveness of 3D and 2D regimens did not directly compare these regimens with any of the comparators listed in the final scope issued by NICE. The company stated that the data for the

3D and 2D regimens came from single treatment arms in the trials and could not be connected through a network to the comparator data. However the ERG commented it would be possible to undertake a network meta-analysis if the results from the ongoing MALACHITE trials (which directly compare 3D with telaprevir regimens) were included. Is a network meta-analysis feasible and appropriate?

Cost effectiveness

- The company did not present cost effectiveness results stratified by whether a person had or did not have cirrhosis. The ERG provided an addendum to its report in which it provided cost effectiveness estimates stratified by cirrhosis status. Given the limited efficacy data available for patients with cirrhosis (1 trial for GT1 and no data for GT4), how robust are the ICERs presented?
- The ERG stated that the baseline characteristics (starting age, weight, sex and fibrosis distribution) for the patient population in the economic model were primarily obtained from other published NICE technology appraisals and were not informed by the baseline characteristics from the 3D and 2D trials. How comparable are the assumed baseline population characteristics used in the economic model with the baseline characteristics of the patients included in the trials?
- The SVR rates for the 3D and 2D regimens and the comparators were based on unadjusted indirect comparisons. The ERG considered that the company could have undertaken a network meta-analysis for the comparators, even if a network meta-analysis for the 3D and 2D regimens was not feasible. How robust are the SVRs from the unadjusted comparisons? Would a network meta-analysis for the comparators be feasible and appropriate?
- The ERG highlighted the lack of trial evidence for 3D and 2D in people who are ineligible for, or intolerant to interferon. The company presented cost effectiveness analyses for both interferon-eligible and interferon-ineligible populations assuming equal effectiveness for both populations.
  - Is it appropriate to use an economic model that was developed for evaluation of interferon-based treatment regimens and which was populated with natural

history data largely derived from people who were interferon-eligible for evaluating treatment in people who are interferon ineligible?

- Is the assumption of equal effectiveness in patients who can or who cannot receive interferon, plausible?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of ABT 450/ritonavir/ombitasvir with or without dasabuvir within its licensed indication for treating chronic hepatitis C.

Note: the remit for this appraisal was formally referred to NICE by the Department of Health before the international non-proprietary name for ABT-450 (that is paritaprevir) was known. The components of co-formulated product were also subsequently reordered.

Table 2 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population(s)	Adults with chronic hepatitis C: • who have not had treatment for chronic hepatitis C before (treatment-naive) • who have had treatment for chronic hepatitis C before (treatment-experienced)	Adults with chronic hepatitis C genotype 1 (GT1) and genotype 4 (GT4): • who have not had treatment for chronic hepatitis C before (treatment-naive) • who have had treatment for chronic hepatitis C before (treatment-experienced)	More specific than the final scope to be in line with the marketing authorisation	The population reflects the potential use of the technology in the NHS and therefore, is appropriate for the appraisal
Intervention(s)	Co-formulated ombitasvir/paritaprevir/ritonavir with or without dasabuvir, co-administered with or without ribavirin	Co-formulated ombitasvir/paritaprevir/ritonavir with (3D) or without dasabuvir (2D), co-administered with or without ribavirin	The company has presented evidence for 2 types of treatment regimens, • 3D regimen for GT1: ombitasvir/ paritaprevir/ ritonavir plus dasabuvir. The company denoted it as 3D because it contains 3 direct acting antiviral drugs namely ombitasvir, paritaprevir and dasabuvir • 2D regimen for GT4: ombitasvir/ paritaprevir/ ritonavir. This regimen is given without dasabuvir and is referred to as 2D because it contains 2 direct acting antiviral drugs (ombitasvir and paritaprevir) Note: Ritonavir is a	The interventions are in line with the final scope and also accurately reflect the specifications in the SPC regarding treatment duration and ribavirin co-administration for different genotype, subtypes and cirrhosis status

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
			pharmacokinetic enhancer for paritaprevir (increases the bioavailability of paritaprevir by inhibiting its metabolism).	
Comparators	• PR (peginterferon alfa and ribavirin) (GTs 1-6) • Telaprevir + PR (for GT1 only) • Boceprevir + PR (for GT1) • Sofosbuvir + R± P (for GTs 1-6) (subject to ongoing NICE appraisal ID654) • Simeprevir +PR (GT 1 or 4) (subject to ongoing NICE appraisal ID668) • Simeprevir + sofosbuvir, ± R (for GTs 1 or 4 and ineligible or intolerant to P) (subject to ongoing NICE appraisal ID668) • Best supportive care (watchful waiting) (GTs 1-6)	For GT1: • Telaprevir + PR • Boceprevir + PR • Sofosbuvir + PR • PR • Best supportive care for whom P is unsuitable For GT4, • PR • Sofosbuvir + PR • Best supportive care for whom P is unsuitable	The company acknowledged that simeprevir + PR is an appropriate comparator (for people who have the G80K polymorphism) but did not present analyses comparing simeprevir regimens with 3D or 2D regimens citing unavailability of the relevant data. For patients in whom P (peginterferon alfa) is unsuitable, the company compared 3D and 2D regimens with best support care noting that NICE did not preliminary recommend sofosbuvir + R or sofosbuvir + simeprevir in this population. For GT1, the company presented analyses comparing 3D regimen with boceprevir + PR and PR regimens however commented that these regimens (boceprevir + PR and PR) are not widely used in clinical practice.	The ERG agreed that there are no publicly available data to inform a robust comparison with simeprevir regimens. The ERG agreed that NICE has not recommended sofosbuvir + R for people in whom P is not suitable. However, for sofosbuvir + simeprevir regimen, NICE has postponed the development of guidance to allow for more data to become available and therefore, sofosbuvir + simeprevir regimen could be recommended in future.
Outcomes	• sustained virological	• SVR at 12 weeks	As specified in the scope	The ERG agreed that SVR at 12

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
	response (SVR) • development of resistance to ombitasvir/ paritaprevir/ritonavir combination therapy • mortality • adverse effects of treatment • health-related quality of life	• development of resistance to 3D or 2D therapy • mortality • adverse effects of treatment • health-related quality of life		weeks is a clinically suitable endpoint because it is used for regulatory approval now and it is highly predictive of SVR at 24 weeks.
Subgroups	If evidence allows the following subgroups will be considered: • Genotype • Co-infection with HIV • Patients with and without cirrhosis • People who have received treatment pre- and post-liver transplant • Response to previous treatment (non-response, partial response, relapsed) • People who are intolerant to or ineligible for interferon treatment,	The decision problem addresses the following sub-groups: • Genotype and sub-genotype • Co-infection with HIV • Patients with and without cirrhosis • People who have received treatment post-liver transplant • Response to previous treatment (non-response, partial response, relapsed) • People who are intolerant to or ineligible for interferon treatment	The company did not present separate economic analyses for people with HIV co-infection noting that SVR was similar in patients with HIV co-infection and patients with mono-infection of hepatitis C virus (HCV)	The ERG agreed with the company's decision for not modelling people with HIV co-infection separately noting that the additional monitoring cost for these patients would not have an important impact on the cost-effectiveness. The ERG noted that a number of other subgroup analyses for SVR outcomes were presented in the GT1 trial results, such as subgroups by gender, race and ethnicity, age, body mass index, fibrosis score, interleukin 28B (IL28B) genotype, diabetes history, HCV RNA level, geographic region, IP-10, and for treatment history.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
				The results of subgroup analyses are presented for the GT1 trials only, as 100% of patients in the 1 GT4 trial achieved SVR12.
Other consideration	If evidence allows the impact of treatment on reduced onward HCV transmission will also be considered	The company did not present data on the impact of treatment on preventing onward transmission of HCV	The company underscored the reduction in the onward transmission as a substantial health-related benefit that is unlikely to be captured in the QALY calculation (see section 4.1.2 (page 51) of the company's submission	

2 The technology and the treatment pathway

Technology

2.1 Co-formulated ombitasvir/paritaprevir/ ritonavir (Viekirax, Abbvie) is a fixed dose combination of 2 direct acting anti-hepatitis C virus drugs (ombitasvir [12.5 mg] and paritaprevir [75 mg]) with ritonavir (50 mg).

- Ombitasvir is an inhibitor of a non-structural viral protein (NS5A), which plays a role in viral genome replication, virus assembly, and modulation of host pathways.
- Paritaprevir is an inhibitor of NS3/4A serine protease which cleaves viral polyprotein after translation.
- Ritonavir is an HIV aspartic protease inhibitor that increases the bioavailability of paritaprevir by inhibiting its metabolism.

2.2 Co-formulated ombitasvir/paritaprevir/ritonavir is given orally as 2 tablets once daily. It has a marketing authorisation in the UK for the treatment of chronic hepatitis C in adults in combination with other medicinal products.

2.3 Dasabuvir (Exviera, Abbvie) is also a directly acting anti-hepatitis C virus drug which inhibits a viral enzyme NS5B that has a role in viral genome replication. It is given orally as 1 tablet (250 mg) twice daily (morning and evening). Dasabuvir has a marketing authorisation in the UK for the treatment of chronic hepatitis C in adults in combination with other medicinal products.

2.4 The summary of product characteristics outlines medicinal products which could be co-administered with ombitasvir/paritaprevir/ritonavir as well as treatment duration for different patient populations defined by genotype, subtypes and the presence or absence of cirrhosis (see Table 3).

Table 3 Treatment regimen and duration of treatment

Patient population	Treatment*	Duration
GT1b, without cirrhosis	ombitasvir/paritaprevir/ritonavir + dasabuvir (3D)	12 weeks
GT1b, with compensated cirrhosis	ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin (3D+R)	12 weeks
GT1a, without cirrhosis	ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin* (3D+R)	12 weeks
GT1a, with compensated cirrhosis	ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin* (3D+R)	24 weeks
GT4, without cirrhosis	ombitasvir/paritaprevir/ritonavir + ribavirin (2D+R)	12 weeks
GT4, with compensated cirrhosis	ombitasvir/paritaprevir/ritonavir + ribavirin (2D+R)	24 weeks
*Note: Follow the GT1a dosing recommendations in patients with an unknown GT1 subtype or with mixed GT1 infection. Follow the same dosing recommendations in patients with HIV-1 co-infection Source: Section 4 of the SPC and table 20 of the company's submission		

Treatment Pathway

2.5 The aim of treatment is to cure the hepatitis C virus (HCV) infection and prevent liver disease progression (cirrhosis), hepatocellular carcinoma (HCC), and HCV transmission. Sustained virological response at 12 weeks after the end of treatment (SVR12) is considered a good indicator of successful treatment. Most patients who achieve SVR12 after the end of treatment maintain their HCV-negative status, have reduced complications from liver disease, and live longer.

2.6 Management of hepatitis C can involve a 'watchful waiting' approach, for those with mild hepatitis C, agreed between the patient and clinician on an individual basis. Once active treatment is required, the options vary according to genotype and treatment experience.

2.7 NICE guidance on hepatitis C (technology appraisal guidance 75 and 106) recommends ribavirin in combination with either peginterferon alfa-2a or peginterferon alfa-2b for people with chronic hepatitis C, regardless of disease severity or genotype. 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.

2.8 NICE technology appraisal guidance 200 recommends that people who have been previously treated with peginterferon alfa and ribavirin or with peginterferon alfa monotherapy have an option to receive further courses of peginterferon alfa and ribavirin. Shortened courses of combination therapy are also recommended as an option for certain people depending on their genotype and their initial response to treatment.

2.9 For people with genotype 1 chronic hepatitis C, who have or have not been previously treated, NICE guidance recommends telaprevir in combination with peginterferon alfa and ribavirin (NICE technology appraisal guidance 252) or boceprevir in combination with peginterferon alfa and ribavirin (NICE technology appraisal guidance 253).

2.10 For people with genotypes 1 and 4 chronic hepatitis C, whose disease has or has not been previously treated, NICE has recommended simeprevir in combination with peginterferon alfa and ribavirin as an option (NICE technology appraisal guidance 331). Simeprevir also has a marketing authorisation in the UK for use in combination with sofosbuvir. However, recommendations for simeprevir in combination with sofosbuvir will be developed in a separate NICE guidance.

2.11 For people with genotypes 1-6 chronic hepatitis C, whose disease has or has not been previously treated, NICE has recommended sofosbuvir in combination with ribavirin, with or without peginterferon alfa, as an option for specific people (NICE technology appraisal guidance 330), chronic hepatitis C as detailed in Appendix B: NICE technology appraisal No. 300 ‘Sofosbuvir for treating chronic hepatitis C’.

2.12 NICE is currently appraising 2 other treatment regimens for CHC. These are ledipasvir-sofosbuvir [ID 742], and daclatasvir [ID 766].

Table 4 Treatment regimens for the populations of interest

Population characteristics			**Recommended 3D/2D regimen**	**NICE-recommended comparators**
Genotype	subtype	Cirrhosis status		
1	1a	Non-cirrhotic	3D+R (12 weeks)	PR TVR+PR BOC+PR SMV+PR SOF+PR
		Cirrhotic	3D+R (24 weeks)	
	1b	Non-cirrhotic	3D (12 weeks)	
		Cirrhotic	3D+R (12 weeks)	
4		Non-cirrhotic	2D+R (12 weeks)	PR SMV+PR
		Cirrhotic	2D+R (24 weeks)	PR SMV+PR SOF+PR
Abbreviations: 3D, ombitasvir/paritaprevir/ritonavir with dasabuvir; 2D, ombitasvir/paritaprevir/ritonavir without dasabuvir; BOC, boceprevir; DCV, daclatasvir; PR, peginterferon and ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir				

Table 5 Technology

	Interventions		Comparators				
	Ombitasvir/paritaprevir/ritonavir (Viekirax)	**Dasabuvir (Exviera)**	**Sofosbuvir (Solvadi)**	**Simeprevir (Olysio)**	**Telaprevir (Incivo)**	**Boceprevir (Victrelis)**	**Peginterferon alfa**
Marketing authorisation	Viekirax (Abbvie) is indicated in combination with other medicinal products for the treatment of CHC in adults. See table 1 of the SPC for recommendations for specific population defined by genotypes and the presence of cirrhosis	Exviera (Abbvie) is indicated in combination with other medicinal products for the treatment of CHC in adults. See table 1 of the SPC for recommendations for specific population defined by genotypes and the presence of cirrhosis	Sovaldi (Gilead Sciences) is indicated in combination with other medicinal products for the treatment of CHC in adults. See table 1 of the SPC for recommendations for specific population defined by genotypes	Olysio (Janssen) is indicated in combination with other medicinal products for the treatment of CHC in adult patients. See table 1 of the SPC for recommendations for specific population defined by genotypes, treatment history and HIV co-infection.	Incivo (Janssen), in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 CHC in adult patients with compensated liver disease (including cirrhosis): - who are treatment-naïve; - who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and	Victrelis (Merck Sharp & Dohme) is indicated for the treatment of CHC genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.	Peginterferon alfa-2a Pegasys (Roche) is indicated in combination with other medicinal products, for the treatment of CHC in patients with compensated liver disease Peginterferon alfa-2b ViraferonPeg (Merck Sharp & Dohme) Is indicated for the treatment of CHC as • Mono-therapy • with ribavirin • with boceprevir and ribavirin

					null responders.		(GT1 only)
Administration method	Oral	Oral	Oral	Oral	Oral	Oral	Subcutaneous
Cost	The cost of 28 days' supply (56 tablets) is £10733.33 excluding VAT. Total cost of a 12 week and a 24 week course are £32200 and £64400 respectively (both excluding VAT: MIMS, February 2015).	The cost of 28 days' supply (56 tablets) is £933.33 excluding VAT. Total cost of a 12 week and a 24 week course are £3100 and £6200 (both excluding VAT: MIMS, February 2015).	The cost is £11,660.98 per 28 tablet pack of 400 mg tablets (excluding VAT, BNF May 2014). The cost of a 12 week course of treatment is £34,982.94 and a 24 week course is £69,965.88 (both excluding VAT) Note The cost does not include the cost for concomitant medications such as ribavirin and peginterferon alfa.	The cost is £1866.50 per pack of 7 tablets (excluding VAT, MIMS online, accessed July 2014). The cost of a 12 week course is £22,398 excluding VAT Note: The cost does not include the cost for concomitant medications such as ribavirin and peginterferon alfa.	Telaprevir has a list price of £1866.50 for a 1-week, 42-tablet pack (excluding VAT; MIMS 2014). This equates to £22,398 for a 12-week course of therapy. Note: The cost does not include the cost for concomitant medications such as ribavirin and peginterferon alfa.	Boceprevir is priced at £2800 for a 28-day, 336-tablet pack (excluding VAT; MIMS 2014) and costs £30,800 for a 44-week course. Note: The cost does not include the cost for concomitant medications such as ribavirin and peginterferon alfa.	The cost of 1 week peginterferon alfa-2a monotherapy (180 micrograms) is £126.91 (excluding VAT; BNF edition 59). The cost of 1 weeks with peginterferon alfa-2b monotherapy is £162.60 (excluding VAT; BNF 59)
See summary of product characteristics for details on adverse reactions and contraindications.							

3 Comments from consultees

3.1 The patient groups stated that some people with CHC do not experience any symptoms, but many others may experience chronic fatigue, mood swings and sexual dysfunction. They also commented that the psychological effect of having CHC can impair people's social life and ability to work and people experience stigma because of CHC's association with drug use. The patient groups stated that people who were infected through the healthcare facilities often feel frustrated because they feel they have not been adequately compensated.

3.2 The patient groups stated that achieving a 'cure' from CHC with consequent improvement in life expectancy, quality of physical, emotional, social, employment and sexual life, is the most important outcome for patients. They also stressed the importance of providing appropriate information to the patients about their condition and available treatment options as well as patients' involvement in the clinical decision making.

3.3 The patient groups were concerned with the available treatment options which include ribavirin and interferon noting that adherence to these regimens is challenging because of insufficient efficacy, side effects and long durations of treatment. They also highlighted the regional variations in the available treatments and support for people with CHC.

3.4 The patient groups expected that since 3D and 2D are all-oral and interferon free regimens and the duration of treatment is shorter, the patient compliance would be better particularly for groups often considered 'difficult to treat' such as prisoners, people who inject drugs and the homeless. The patient groups expressed that people living with CHC fear that interferon-free therapy will be denied to them on the grounds of affordability.

3.5 No comments were received from professional groups.

4 Clinical-effectiveness evidence

Overview of the clinical trials

Genotype 1

4.1 The company's submission included 8 completed trials for 3D regimens in patients with GT1 CHC (see Figure 1 of the company's submission, page 60)

- 6 phase III trials (SAPPHIRE-I, SAPPHIRE-II, TURQUOISE-II, PEARL-II, PEARL-III and PEARL-IV)
- 2 phase II trials (AVIATOR and M14-103). The company commented that AVIATOR and M14-103 were included for completeness and should be considered as supplementary evidence as these trials were not used in the economic model and do not form part of the pivotal trials for the European Medicine Agency (EMA) regulatory submission.

The company stated that the GT1 CHC trials were designed in conjunction with the EMA and the US Food and Drug's Administration where it was deemed that comparisons with historical cohorts of telaprevir were sufficient to demonstrate efficacy.

4.2 At clarification stage, the company provided academic in confidence results from 2 additional ongoing open-label randomised control trials (MALACHITE I and MALACHITE II) comparing 3D+R with telaprevir +PR in patients with GT1 CHC.

4.3 The company also included preliminary results from 2 ongoing trials, evaluating 3D regimens in patients co-infected with HIV-1 (TURQUOISE I) and in patients who had received a liver transplant (CORAL I).

4.4 The 6 completed trials included in the company's submission did not compare 3D regimens directly with any of the comparators listed in the scope. The trials were designed to compare the primary outcome (sustained virological response [SVR]) achieved by 3D regimens to the SVR reported in previously conducted trials of telaprevir +PR regimens (ILLUMINATE, ADVANCED and REALISE) in similar populations and to demonstrate non-inferiority and subsequent superiority of 3D regimens. The patient population and trial design of the phase III trials are summarised below (section 4.6 to 4.9 and Table 6). For further details of the trials, see tables 26-29, pages 68-91 of the company's submission.

Genotype 4

4.5 The company's submission included 1 completed phase II trial (PEARL I) for the 2D regimen in patients with GT 4 (see Figure 1 of the company's submission, page 60).

Evidence in people with Genotype 1

SAPPHIRE I and SAPPHIRE II trials

4.6 SAPPHIRE I and SAPPHIRE II were randomised placebo control trials conducted in North America, Europe, and Australia, in patients with GT1a and GT1b without cirrhosis. SAPPHIRE I included treatment naïve patients and SAPPHIRE II included treatment experienced patients. Patients were randomly assigned in a 3:1 ratio to receive a 3D+R regimen (n=473 SAPPHIRE I, n= 297 SAPHIRE II) or placebo (n=158 SAPPHIRE I, n=97 SAPHIRE II) during the 12-week double-blind period. Randomisation was stratified according to HCV genotype (1a vs. non-1a) and IL28B genotype (CC vs. non-CC). Patients receiving placebo during the double-blind period, were treated with 3D+R for 12 weeks in an open-label fashion after the end of double-blind period.

TURQUOISE-II

4.7 TURQUOISE-II was a multicentre, randomised open-label trial conducted in North America and Europe. It recruited treatment naïve and treatment experienced patients with GT1 CHC with compensated cirrhosis. The trial compared a 12 week regimen of 3D+R (n=208) with a 24 week regimen of 3D+R (n=172). Patients were randomly assigned in a ratio of approximately 1:1 to the 12-week or 24-week treatment group. Treatment naïve patients were stratified according to HCV sub-genotype (1a vs. 1b) and interleukin 28B (IL28B) genotype (CC vs. non-CC). Treatment experienced patients were stratified according to HCV sub-genotype and by type of nonresponse to previous treatments (null response, partial response or relapse).

PEARL II, PEARL III and PEARL IV

4.8 PEARL II, PEARL III and PEARL IV were multicentre, randomised trials comparing a 3D regimen for 12 weeks with a 3D+R regimen for 12 weeks in patients with different subtypes of GT1.

4.9 PEARL II and III recruited patients with GT1b CHC. PEARL II recruited treatment experienced patients (n=91 3D+R group, n=95 3D group) while PEARL III recruited treatment naïve patients (n=210 3D+R group, n=209 3D group). In PEARL II, patients were stratified according by type of nonresponse to previous treatments (null responders, partial responders, and relapsers) while in PEARL III patients were stratified according to IL28B genotype (CC vs. non-CC)

4.10 PEARL IV recruited patients with GT1a CHC who were treatment naïve. Patients were stratified according to IL28B genotype (CC vs. non-CC) were randomly assigned in a 1:2 ratio to receive either 3D+R (n=100) or 3D+placebo (n=205).

MALACHITE I and MALACHITE II trials

4.11 MALACHITE I and MALACHITE II trials are ongoing head-to-head, randomised, open-label, active-controlled trials comparing the safety and efficacy of 3D with or without R compared with telaprevir +PR. MALACHITE I included treatment naïve patients and MALACHITE II included treatment experienced patients. For further details of the ongoing trials, see the company's response to clarification, section 9.2 page12-15.

TURQUOISE I and CORAL I

4.12 TURQUOISE I is an ongoing open-label randomised trial evaluating 3D + RBV for 12 or 24 weeks in patients with GT1 CHC who are also co-infected with HIV including those with compensated cirrhosis (estimated n=300).

4.13 CORAL-I is an ongoing, open-label, multi-centre study evaluating the safety and efficacy of 3D with and without ribavirin in adult liver transplant recipients with recurrent GT1 infection (estimated n=70). The company's submission included interim results from TURQUOISE I and CORAL I trials (see section 6.5.10 of the company's submission page 181).

Table 6 Summary of patient population and treatment regimens compared in the phase III studies for patients with GT1 CHC

Phase III studies	Regimens studied	Genotype-subtype		Treatment history		Cirrhosis status	
		GT1a	GT1b	Naïve	Experienced	Non-cirrhotic	Cirrhotic
SAPPHIRE I	3D+R vs placebo	Both		✓		✓	
SAPPHIRE II	3D+R vs placebo	Both			✓	✓	
TURQUOISE II	3D+R 12 weeks vs 24 weeks	Both		Both			✓
PEARL II	3D+R vs 3D		✓		✓	✓	
PEARL III	3D+R vs 3D		✓	✓		✓	

PEARL IV	3D+R vs 3D	✓		✓		✓	
MALACHITE I	3D+R & 3D vs Telaprevir +PR	Both		✓		✓	
MALACHITE II	3D+R vs Telaprevir +PR	Both			✓	✓	
Treatment duration was 12 weeks unless stated otherwise Adapted from table 5, page 32 of the ERG report							

4.14 Among the phase 3 trials evaluating 3D regimens in people with GT1 CHC, patient baseline characteristics varied as follows:

- mean age from 48.4 years (PEARL III, 3D+RBV treatment arm) to 57.1 years (TURQUOISE II, 3D 12 week treatment arm).
- proportion of men from approximately 45% (PEARL III) to approximately 70% (TURQUOISE II).
- proportion of white people 83.4% (PEARL IV, 3D treatment arm) to 95.7% (TURQUOISE II, 3D 12 week treatment arm).
- proportion of people with moderate fibrosis (fibrosis score F2 or F3) 23.3% (SAPPHIRE I, 3D+RBV treatment arm) to 37% (PEARL IV, 3D+RBV treatment arm).
- proportion of people with IL28B CC gene 7.2% (SAPPHIRE II, placebo treatment arm) to 31.6% (SAPPHIRE I, placebo treatment arm).

For further details of the baseline patient characteritics across the randomised groups in the GT1 CHC trials, see table 33 of the company's submission, page 119).

Evidence in people with Genotype 4

4.15 The evidence for the effectiveness of the 2D regimen in people with GT4 CHC without cirrhosis came from a phase II, multinational, open-label, randomised trial (PEARL I). PEARL I evaluated 12 week regimens of 2D

in treatment naïve patients (n=44), and 2D+R in both groups of treatment naïve (n=42) and treatment experienced (n=49) patients. In other treatment arms, PEARL I included people with GT1b CHC only, however the company did not include the results from these treatment arms in its submission because it is outside the marketing authorisation. In contrast to the phase III trials of 3D regimen, there was no planned historical comparison with telaprevir in the PEARL I study. For further details of the PEARL I trial, see table 31on page 91 of the company's submission.

4.16 The company did not include any clinical evidence to support the licensed use of 2D+R regimen for 24 weeks in patients with GT4 CHC with cirrhosis. The company acknowledged that there are no trial data available on the treatment of patients with cirrhosis. The EMA noted that data from PEARL I trial demonstrated the efficacy of 2D regimen for 24 weeks in patients with GT1b CHC with cirrhosis and concluded that efficacy of 2D + R for 24 weeks in patients with GT4 CHC with cirrhosis was likely to be the same. The rationale given was the similarity of the in vitro effects and pharmacodynamics for both component of the 2D (paritaprevir and ombitasvir) on GT1b and GT4 HCV.

4.17 The results for the 2D+R for 24 weeks treatment arm for patients with GT1b CHC from the PEARL I trial were not included in the company's submission, however the EPAR reports an SVR of 97% (see section 2.5.2.3, table 21, page 110).

4.18 The baseline patient characteristics of patients with GT4 CHC across the 3 GT4 treatment groups in the PEARL I trial ranged as follows; men 54.5% to 73.5%, age 44.2 to 50.9 years, fibrosis score F2 or F3 13.6% to 32.6%, IL28B CC genotype subgroup 12.2% to 27.3%. For furthers of the baseline patient characteristics, see table 34, page 123 of the company's submission.

ERG comments

4.19 The ERG was satisfied overall with the literature searches conducted by the company but noted that one included phase II study (AVIATOR) did not meet the inclusion criteria because in that study, dasabuvir (a component of the 3D regimen), was administered at a dose (400 mg twice daily) higher than the licensed dose (250 mg twice daily).

4.20 The ERG was concerned with the lack of a randomised comparison of 3D and 2D regimens, and commented that all the completed trials included in the company's submission provided essentially non-randomised, observational data for the primary outcome of SVR12 (from individual trial arms or subgroups).

4.21 The ERG commented that the company did not provide sufficient detail on the similarity of patients in the 3D trials to those in the trials of telaprevir (ADVANCE, ILLUMINATE and REALIZE) used for the historical comparison or the other comparators relevant to the decision problem. During the clarification stage, the company stated that it was not possible to examine the baseline characteristics for the specific matched historical control rates, as the baseline data for telaprevir were not available at the disaggregated level.

4.22 The ERG commented that there were higher proportions of patients with mild fibrosis (that is fibrosis scores of F0 and F1) in the 3D trials than in the historical comparator telaprevir trials, which may have biased the SVR estimates in favour of 3D.

Table 7 Trial arms or subgroups; that informed efficacy for treatment regimens stipulated in the SPC

SPC recommendation			Trial evidence[a]			
Patient population	**Treatment**	**Duration, weeks**	**Trial**	**Genotype in trial**	**Comparison in trial**	**Trial arm or subgroup meeting licence**
GT1b without cirrhosis	3D	12	PEARL II	1b	3D+RBV vs 3D	Treatment arm with 3D, n=91
			PEARL III	1b	3D+RBV vs 3D	Arm with 3D, n = 209
GT1b with	3D + RBV	12	TURQUOISE	1a and 1b	3D+RBV 12	Subgroup with

SPC recommendation			Trial evidence[a]			
Patient population	**Treatment**	**Duration, weeks**	**Trial**	**Genotype in trial**	**Comparison in trial**	**Trial arm or subgroup meeting licence**
cirrhosis			II		weeks vs 24 weeks	GT1b in the 12 weeks treatment arm ,n=68/208
GT1a without cirrhosis	3D + RBV	12	SAPPHIRE I	1a and 1b	3D+RBV vs placebo	Subgroup with GT1a, n=322/473
			SAPPHIRE II	1a and 1b	3D+RBV vs placebo	Subgroup with GT1a, n=173/297
			PEARL IV	1a	3D+RBV vs 3D	Treatment arm with 3D+RBV, n=100
			M14-103	1a and 1b	3D + RBV (single arm trial)	Subgroup with GT1a, n=[redacted][b]
GT1a with cirrhosis	3D + RBV	24	TURQUOISE II	1a and 1b	3D+RBV 12 weeks vs 24 weeks	Subgroup with GT1a in the 24 weeks treatment arm, n=121/172
GT4 without cirrhosis	2D + RBV	12	PEARL I	4	2D+RBV vs 2D (Naive) 2D+RBV (Experienced)	Treatment arms with 2D+RBV, Naive n=42, Experienced, n=49
GT4 with cirrhosis	2D + RBV	24	No data (see above section 4.14)			

[a] Treatment duration in trials was 12 weeks unless stated otherwise.
[b] The company provided the results of a subgroup analysis of SVR12 by HCV sub-genotype, in response to a clarification question.
Based on the table 6 of the ERG report page number 33.

Clinical trial results

Genotype 1

SVR

4.23 The primary outcome in all of the included trials was SVR12. It was defined as an HCV RNA level of less than 25 IU per millilitre at 12 weeks after the end of the treatment.

4.24 The results for the 3D and 3D+R regimens from the trial arms or subgroups from the 6 completed trials by the patient populations

specified in the summary of product characteristics are presented in Table 8.

Table 8 SVR12 outcome from trial arms or subgroups where treatment matches licensed indication

Patient population	Treatment	Duration weeks	Study	SVR12 (n/N)	%SVR (95% CI)	%SVR12 in historical control (telaprevir) (95% CI)
GT1b, without cirrhosis	3D	12	PEARL III (naïve)	209/209	100.0 (98.2-100.0)	80 (75-84)
			PEARL II (experienced)	91/91	100 (95.9-100.0)	69 (62-75)
GT1b, with compensated cirrhosis	3D+R	12	TURQUOISE II	67/68	98.5 (95.7-100.0)	Not available
GT1a, without cirrhosis	3D+R	12	SAPPHIRE I (naïve)	308/322	95.7 (93.4-97.9)	72 (68-75)
			PEARL IV (naïve)	97/100	97.0 (93.7-100.0)	72 (68-75)
			SAPPHIRE II (experienced)	166/173	96.0 (93.0-98.9)	59 (53 to 65)
GT1a, with compensated cirrhosis	3D+R	24	TURQUOISE II	115/121	95.0 (91.2-98.9)	Not available
Adapted from table 10, page 53 of the ERG report. For the SVR rates in other trial arms (unlicensed regimens), see the company's submission tables 38 (page 153), 40 (page 158), 42 (page 163), 45 (page 168), and 47 (page 170).						

4.25 The SVR results from ongoing studies are summarised in Table 9

Table 9 Interim results from ongoing studies

Patient population	Treatment	Duration weeks	Study	SVR12 (n/N)	%SVR (95% CI)	%SVR12 in control (telaprevir)
HCV GT1/HIV-1 co-infected	3D+R	12	TURQUOISE-I	29/31	93.5 (79.3-98.2)	
		24	TURQUOISE-I	29/32	90.6	
GT1 post-transplant	3D+R	24	CORAL I	33/34	97.1	

patients						
GT1a without cirrhosis (naïve)	3D+R	12	MALACHITE I	[redacted]	[redacted]	[redacted]
GT1b without cirrhosis (naïve)	3D	12	MALACHITE I	[redacted]	[redacted]	[redacted]
	3D+R	12	MALACHITE I	[redacted]	[redacted]	
GT1 (experienced)	3D+R	12	MALACHITE II	[redacted]	[redacted]	[redacted]
Based on the company's submission table 54 -55 (page 180, 182), and the company's response to clarification letter table 8-9 (page 14-15)						

Secondary outcomes

4.26 Virologic failure (during treatment), relapse (post-treatment), and normalisation of the alanine aminotransferase level were the secondary outcomes in the trials. Virologic failure and relapse were reported in all completed trials. The incidence of virologic failure was consistently low, zero in many trial arms, with the maximum incidence of 2.9% reported in the 3D for 12 weeks treatment arm of PEARL IV trial; in treatment naïve patients with GT1a CHC without cirrhosis (an unlicensed treatment for that population). In the trial arms or the trial arms with a subgroup meeting the licensed indication, the highest on-treatment virologic failure rate (1.7%) was in the 3D+R, 24 weeks treatment arm of the TURQOUSIE II trial in patients with GT1 CHC with cirrhosis. Relapse rate following treatment were also low, zero in many trials, and the highest rate of 5.9% was reported for the 3D+R in the 12 weeks treatment arm of the TURQOUSIE II trial in patients with GT1 CHC with cirrhosis.

4.27 Only SAPPHIRE I and SAPPHIRE II reported results on the normalisation of alanine aminotransferase levels and these were for the whole trial population. The treatment (3D+R for 12 weeks) which was evaluated in the 2 trials is the licensed treatment only for those with GT1a CHC which consisted of 68% and 58% of the total patients

included in the SAPPHIRE I and SAPPHIRE II trials respectively. In both trials the proportion of patients whose alanine aminotransferase level normalised was statistically significantly higher ($p<0.001$) in the 3D + RBV group than in the placebo group (SAPPHIRE I 97.0% compared with 14.9 %; SAPPHIRE II 96.9% compared with 12.8%).

Health related quality of life

4.28 The completed phase III trials also reported data on health-related quality of life which was measured using the SF36 physical component score (PCS) and mental component score (MCS), the EQ-5D-5L health index score and visual analogue score, and the HCV-PRO (a new patient reported outcome tool specific for CHC comprising 16 items focusing physical health, emotional health, productivity, social interactions, intimacy and perception).

4.29 The results of the health-related quality of life outcome measures were reported as mean change from the baseline to the final treatment visit and to the 12 week post treatment period (see table 39, 41, 44, 46, 48 and 50 of the company's submission). In general, no statistically significant differences for mean change from baseline to the final treatment period visit or to post-treatment week 12 were observed between treatment arms in most of the trials for most of the patient reported outcome measures. The statistically significant difference were reported in;

- HCV-PRO scores, change from baseline to the final treatment visit between the [redacted].
- SF-36 mental component score from baseline to the final treatment visit was observed between the

[redacted]

- EQ-5D-5L VAS score from baseline to the final visit between [redacted].

4.30 [redacted]

4.31 The EQ-5D-5L health index score from the trials were used to inform the utility values in the economic model and are summarised in Table 10. The EQ-5D-5L health index scores have been obtained using country specific algorithms to cross-walk the 5L values to the 3L tariff scores, the US crosswalk to convert the 5L values to 3L has been used where an individual country specific crosswalk was not available.

Table 10 EQ 5D 5L index score

		N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
Genotype 1, treatment naive, non-cirrhotic	**SAPPHIRE I** (GT1a and b)	**3D + R for 12 weeks** (licensed treatment for n=322 GT1a only)			Placebo		
	Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Final post-treatment visit	[redacted]		[redacted]	[redacted]		
	PEARL IV (GT1a)	**3D + R for 12 weeks**			3D for 12 weeks (unlicensed regimen)		
	Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Post-treatment week 12	[redacted]		[redacted]	[redacted]		[redacted]
	PEARL III (GT1b)	3D + R for 12 weeks (unlicensed regimen)			**3D for 12 weeks**		
	Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Post-treatment week 12	[redacted]		[redacted]	[redacted]		[redacted]
Genotype 1, treatment experienced,	**SAPPHIRE II** (GT1a and b)	**3D + R for 12 weeks** (licensed treatment for n =173 GT1a only)			Placebo		

non-cirrhotic	Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Final post-treatment visit	[redacted]		[redacted]	[redacted]		
	PEARL II (GT1b)	3D + R for 12 weeks (unlicensed regimen)			**3D for 12 weeks**		
	Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Post-treatment week 12	[redacted]		[redacted]	[redacted]		[redacted]
Genotype 1, compensated cirrhosis (treatment naive & treatment experienced)	**TURQUOISE II** (GT1a and b)	**3D + R for 12 weeks** (licensed treatment for n=68 GT1b only)			**3D + R for 24 weeks** (licensed treatment for n=121 GT1a only)		
	Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Post-treatment week 12	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Treatments arms evaluating recommended regimens in the SPC are in bold.							

Subgroups

4.32 The company presented sub-group analyses for some trials evaluating 3D regimens in patients with GT1 CHC (see figures 13-14 [page 156, 160], and table 43 [page 165] of the company's submission). Subgroup analyses did not show any statistically significant difference in terms of SVR12 between subgroups with different demographic characteristics such as age, gender, race, and ethnicity.

4.33 For subgroups categorised on the basis of difficulty to achieve response, the company compared pooled SVR data for 3D regimens and compared it with SVRs reported in the literature for PR, telaprevir +PR (ADVANCE, ILLUMINATE and REALIZE), boceprevir +PR (SPRINT-2), sofosbuvir +PR (NEUTRINO) and simeprevir +PR (QUEST 1, QUEST 2, ATTAIN). These 4 patients subgroup were defined as follows;

- treatment naïve people without cirrhosis (considered easiest to treat group),
- treatment naïve people with cirrhosis,

- treatment experienced people who were classified as null responders, without cirrhosis,
- treatment experienced people who were classified as null responders, with cirrhosis (considered most difficult to treat group),

4.34 The results for these subgroup analyses are provided in Table 11. From the data the company inferred that in contrast to the comparator regimens the effectiveness of 3D regimen was not affected by treatment history, previous response and presence of cirrhosis.

Table 11 Treatment-specific impact of certain disease characteristics on ability to achieve SVR for different treatment

	SVR % (n/N)					
Treatment	**3D +/-R**	**PR**	**TPV + PR**	**BOC + PR [a]**	**SOF + PR [b]**	**SIM + PR**
GT1 naïve, no cirrhosis (F0-F3)	96.8 (611/631)	44.4 (151/340)	75.4 (258/342)	65.9 (222/337)	91.7 (220/240)	81.9 (377/460)
GT1 naïve, cirrhotics (F4)	96.2 (75/78)	33.3 (7/21)	61.9 (13/21)	31.3 (5/16)	80.8 (42/52)	60.4 (29/48)
GT1 null responders, no cirrhosis (F0-F3)	96.6 (115/119)	3.7 (1/27)	34.8 (16/46)	-	-	50.3 (NR)
GT1 null responder cirrhotics (F4)	95.5 (64/67)	10.0 (1/10)	19.2 (5/26)	-	-	24.6 (NR)

[a] boceprevir + PR was not studied in HCV GT1 null responders.
[b] sofosbuvir + PR was not studied in treatment-experienced HCV GT1 patients.

Data for 3D are pooled for the relevant sub-group across all trials.
Data for PR for naïve and experienced patients from comparator arms of the telaprevir trials ADVANCE and REALIZE, respectively.
Data for telaprevir for naïve patients and experienced patients from ADVANCE and REALIZE respectively.
Data for boceprevir from SPRINT-2
Data for sofosbuvir from NEUTRINO
Data for simeprevir for naïve patients from QUEST-1 and QUEST-2 (Lancet, Manns et al, 2014), and data for treatment-experienced patients from ATTAIN (the company's submission to NICE).

Reproduced from Table 58, page 119 of the company submission

Genotype 4

4.35 Results from the 2 treatment arms of PEARL I trial that evaluated the licensed regimen (2D+R) in patients with GT4 CHC are summarised in Table 12.

Table 12 Results from the relevant arms of PEARL I (that evaluated 2D+R in patients with GT4 HCV [non-cirrhotic])

Outcome	Treatment history	% (n/N)	95% Confidence interval I
SVR12	Naïve	42/42 (100%)	91.6-100
	Experienced	49/49 (100%)	92.7-100
SVR24	Naïve	41/42 (97.6%)	87.4-99.9
	Experienced	Not reported	
Virologic failure	Naïve	0/42	
	Experienced	0/49	
Relapse	Naïve	0/42	
	Experienced	0/49	
Based on table 56, page 184 and text on page 185 of the company's submission			

4.36 PEARL I also reported the effect of 2D regimens on the health related quality of life as mean change from baseline to final treatment visit and post-treatment week 24 in the EQ-5D-5L health index score and visual analogue score, and the HCV-PRO score.

4.37 The results (see table 57 of the company's submission) showed that the 2D+R regimen was associated with numerical improvement from baseline in most of the reported health-related quality of score at final treatment visit and post-treatment week 24.

4.38 All patients with GT4 treated with 2D + RBV in PEARL I trial, achieved SVR12 (100%), and therefore the SVR12 rate did not differ across subgroups.

ERG comments

4.39 The ERG commented that in some trials (for example SAPPHIRE I and SAPPHIRE II) only a subgroup provided the efficacy data on the licensed regimen and it is unlikely to be powered to demonstrate non-inferiority and superiority over historical control (telaprevir) because power calculation were based on the sample sizes of the whole trial population.

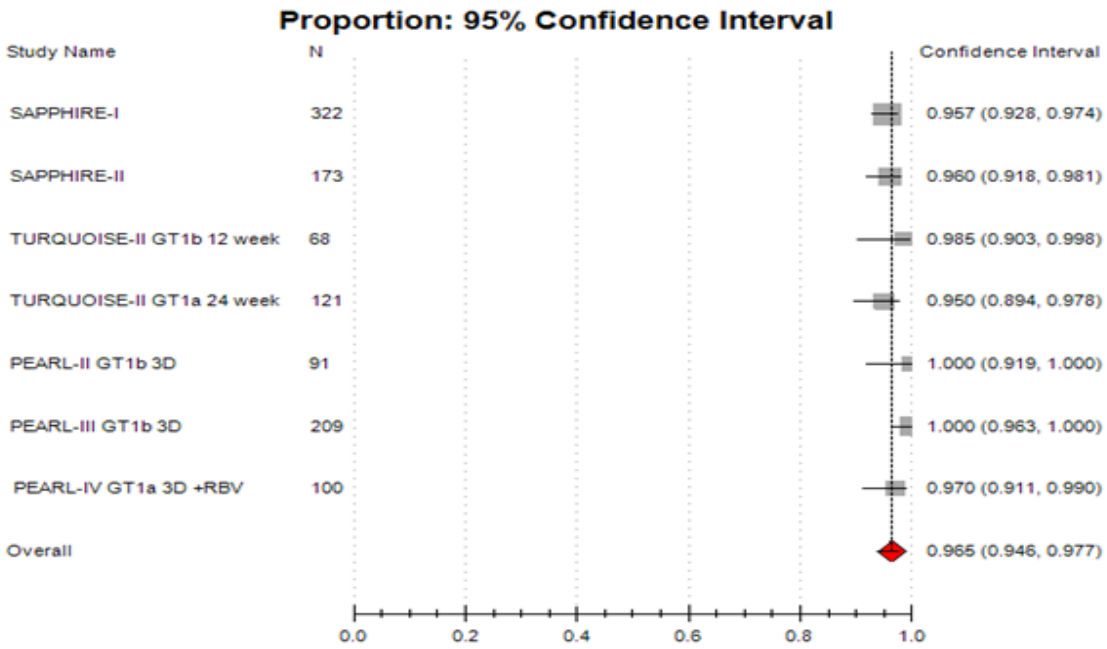
Meta-analyses

4.40 To combine the results from trials evaluating the 3D regimens in GT1 CHC patients, the company used a software (Meta-Analyst) which allows pooling from single arm studies. The company presented 3 meta-analyses, combining SVR12 using random effect model, as follows:

- all active treatment arms in completed phase III clinical trials (SAPPHIRE I SAPPHIRE II, PEARL II, PEARL III, PEARL IV and TURQUOISE II) plus 1 phase II study, M14-103 (see figure 17,page 189 of the company's submission),
- all treatment arms in the completed phase III trials in line with the licence for 3D (see figure 18, page 190 of the company's submission),
- all active treatment arms in the GT1 CHC clinical trial programme, including from dose finding phase II AVIATOR and interim results of 2 ongoing studies, TURQOUISE-1 and CORAL-I (see figure 19, page 192 of the company's submission).

4.41 Meta-analysis of the trial treatment arms, which evaluated 3D regimens in line with the marketing authorisation, resulted in the pooled SVR of 96.5% (CI 94.6 to 97.7%). See Figure 1.

Figure 1 SVR12 rates from the completed phase III trials in line with the licence for 3D in GT1 CHC



ERG comments

4.42 The ERG commented that the meta-analysis that pooled data from study treatment arms that are in line with the licence for the 3D regimen is the most appropriate for this appraisal (see Figure 1). The ERG noted that the company only presented results from the random effect model. The ERG re-ran the meta-analysis using an alternative software package and obtained similar results (random effects model 96.5% 95% CI 94.6 to 97.7, fixed effect model 96.2% 95% CI 94.7 to 97.3).

4.43 The ERG commented that the meta-analysis only provided illustrative information about the average efficacy of the 3D regimens across a range of the licensed treatment regimens in patients with GT1 CHC and noted that the company did not use the meta-analysis findings for economic analyses.

Indirect comparison/ Mixed treatment comparison

4.44 The company stated that a network meta-analysis (NMA) to generate relative estimates of efficacy for 3D and 2D regimens compared with the comparators outlined in the decision problem was not feasible because:

- most of the efficacy data for the 3D and 2D regimens are from single treatment arms of the trials,
- including adjustment factors into an NMA treatment response model was problematic,
- many of the predictive factors had an effect on specific treatment, making results of an indirect comparison difficult to interpret. For example simeprevir is less effective in patient with Q80K polymorphism (see sections 6.7.1 to 6.7.3 of the company's submission).

ERG comments

4.45 The ERG agreed that it was not possible to conduct a robust NMA with the trials included in the company's submission. However, it commented that an NMA of the comparator treatments would have been preferable for estimating effectiveness of the comparator treatments for use in the economic analyses. The ERG also noted that it would be possible to conduct an NMA for the population included in the ongoing MALACHITE trials (which directly compare 3D regimens with telaprevir regimens).

Adverse effects of treatment

4.46 The company presented safety data from all included trials in its submission. A summary of the adverse events from trial treatment arms/subgroups relevant to the marketing authorisation is presented in Table 13.

Table 13 Summary of adverse event from trial treatment arms/subgroups of relevant to marketing authorisation

Study	Regimen	Duration (weeks)	Any AE, (%)	AE leading to dis-continuation of study drug, (%)	Serious AE, (%)
Genotype 1, treatment naive, non-cirrhotic (Table 59 p. 202 and Table 63 p. 210 of the company's submission)					
SAPPHIRE I (GT1a and b) licensed for GT1a only (n=322/473)	3D+R	12	87.5	0.6	2.1
PEARL IV (GT1a) (n=100)	3D+R	12	92	2	3
PEARL III (GT1b) (n=209)	3D	12	67	0.5	1.9
Genotype 1, treatment experienced, non-cirrhotic (Table 60 p. 204 and Table 62 p. 207 of the company's submission)					
SAPPHIRE II (GT1a and b) licensed for GT1a only (n=173/297)	3D+R	12	91.2	1.0	2.0
PEARL II (GT1b) (n=95)	3D	12	77.9	0	2.1
Genotype 1, treatment naive & treatment experienced, compensated cirrhosis (Table 61 p. 205 of the company's submission)					
TURQUOISE II (GT1a and b)	3D+R	24 licensed only for GT1a n=64/172	90.7	2.3	4.7
		12 licensed only for GT1b n=46/208	91.8	1.9	6.2
Genotype 4, treatment naïve non-cirrhotic (Table 66 p. 215 of the company's submission)					
PEARL I (n=42)	2D	12	88.1	0	0

Study	Regimen	Duration (weeks)	Any AE, (%)	AE leading to dis-continuation of study drug, (%)	Serious AE, (%)
Genotype 4, treatment experienced non-cirrhotic (Table 66 p. 215 of the company's submission)					
PEARL I (n=49)	2D	12	87.8	0	0
AE; adverse event, A severe AE was defined as one that caused considerable interference with the usual activities of the patient and that may have been incapacitating or life-threatening					

4.47 The most frequently reported adverse events in the trials were fatigue, headache, nausea, pruritus, insomnia, irritability, diarrhoea, anaemia, asthenia, shortness of breath, cough, muscle ache, itching and rash.

5 Cost-effectiveness evidence

Model structure

5.1 The company provided a Markov state-transition model estimating the cost-effectiveness of 3D and 2D regimens for patients with GTI CHC and GT4 CHC respectively. The structure of model was adapted from the model used in other NICE technology appraisals (TA106 and TA200). The model simulated the lifetime disease progression of persons with chronic HCV infection (see Figure 2 for the schematic of the model). The model adopted a lifetime horizon (70 years) and a cycle length of 1 year. The model applied half-year cycle corrections. The cost was considered from the perspective of NHS and Personal Social Services and all future costs and outcomes (QALYs) were discounted at 3.5% in the base case.

5.2 The model had 6 health states indicating progressive liver disease, 3 health states representing recovered states and 1 all absorbing death state.

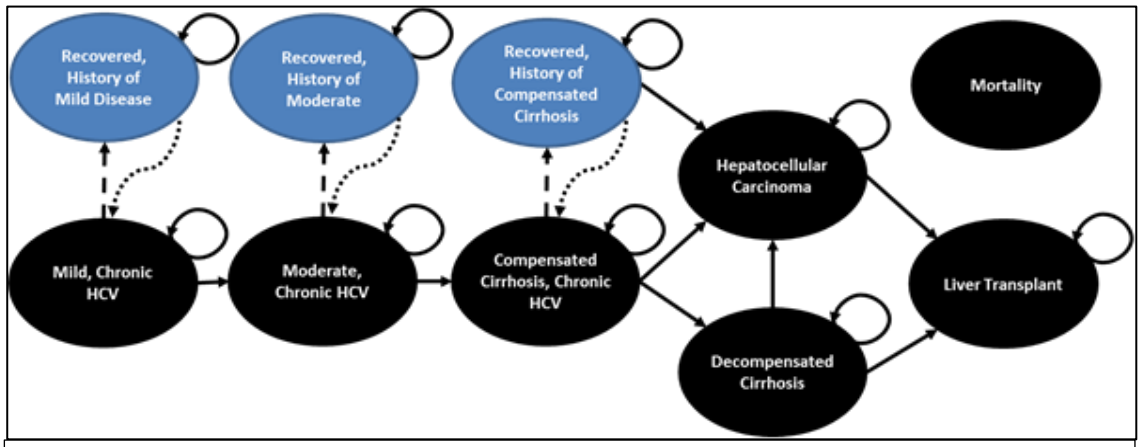
Health states indicating progression of the disease:

1. mild chronic HCV; defined by fibrosis Metavir[1] score F0-F1,
2. moderate chronic HCV; defined by Metavir score F2-F3,
3. compensated cirrhosis; defined by Metavir score F4,
4. decompensated cirrhosis (DCC),
5. hepatocellular carcinoma (HCC) and
6. liver transplant.

Health states representing recovered (SVR) states:

1. recovered, history of mild disease,
2. recovered, history of moderate disease; and
3. recovered, history of compensated cirrhosis.

Figure 2 Model schematic



Arrows represent permissible transitions between health states.

- Hashed arrows depict the possibility of an SVR.
- Dotted arrows depict a potential reinfection.

Death is possible from any health state. Liver death is possible from decompensated cirrhosis, hepatocellular carcinoma, and/or liver transplant

[1] METAVIR is a system used to assess inflammation and fibrosis by histopathological evaluation of a liver biopsy of patients with hepatitis C. The grade indicates the activity or degree of inflammation, and the stage represents the amount of fibrosis or scarring. F0=no fibrosis. F4=cirrhosis.

ERG comments

5.3 The ERG commented that in general, the modelling approach by the company was reasonable and consistent with the evidence-base.

Model details

Modelling of natural history of the disease

5.4 It was assumed in the model that the natural history of genotype 1 and 4 were similar. On entry, the model distributed hypothetical patients across 3 disease states based on progression of the fibrosis (mild, moderate or compensated cirrhosis). Patients could move to recovery states if they responded to treatment and recovery state depended on the disease state prior to treatment. A patient in the recovery states did not face a probability of disease progression. However re-infection with CHC was included in the model, as a constant risk.

5.5 Patients who did not respond to treatment could stay in the same disease state or progressed through disease states (from mild to moderate to compensated cirrhosis, depending on their initial state and rates of fibrosis progression). Patients with compensated cirrhosis could progress to any of 3 advanced liver disease states (decompensated cirrhosis [DC], liver transplant and hepatocellular carcinoma [HCC]). Patients with HCC could also receive liver transplants. Patients in all states could die but DC, HCC and liver transplant states had an additional risk of death from liver disease.

5.6 The economic model assumed the same transition probabilities for both genotypes CHC. Most of the transition probabilities applied within the model for progressive liver disease were sourced from the model developed alongside the UK Mild Hepatitis C trial or to the models developed to inform other NICE technology appraisals (TA106 and TA200) or both. For details of the transition probabilities used in the model, see table 37, page 95 of the ERG report.

Modelled population

5.7 The company modelled treatment-naïve and treatment-experienced patients separately. The patients were further divided by sub-types (GT1a and GT1b), stage of fibrosis (mild, moderate and cirrhosis), and eligibility for treatment with peginterferon. The baseline characteristics such as age, weight, sex and distribution of patients across stages of liver disease was based on a clinical audit of patients attending a liver clinic at a London teaching hospital for treatment of their CHC which was used in the economic models developed for NICE Technology appraisal 106 and 200. Seventy percent of the modelled population were male and the average age of treatment-naïve and treatment-experienced patients at baseline was 40 and 45 years respectively. Baseline characteristic of the modelled population are summarised in Table 14. In the base-case analyses, the company presented results for 4 patient populations (all of them assumed to be eligible for interferon treatment) based on the genotype and prior treatment history as follows:

- GT1, treatment-naïve, interferon eligible patients,
- GT1, treatment-experienced (overall) interferon eligible patients,
- GT4, treatment-naïve, interferon-eligible patients (non-cirrhotic only),
- GT4, treatment-experienced (overall) interferon eligible patients (non-cirrhotic only),

Note that the company did not present any economic analysis in patients with GT4 CHC with cirrhosis.

5.8 The company also presented results for interferon ineligible patients (under subgroup analyses) for 3 groups that included treatment naïve and treatment experienced patients with GT1 CHC as well as for

treatment naive patients with GT4 CHC without cirrhosis (see tables 150-152 page 441 of the company's submission).

Table 14 Baseline characteristics of the modelled population

Baseline characteristics	Base Case Value
Proportion of GT1 patients who are GT1a	68.8%
Distribution of patients by prior non-response	
Null response	30.0%
Partial response	30.0%
Prior relapse	40.0%
Initial Fibrosis Distribution (GT1treatment-naïve and GT4)	
Mild	46.0%
Moderate	44.0%
CC (Chronic HCV)	10.0%
Initial Fibrosis Distribution (GT1 treatment-experienced)	
Mild	33.0%
Moderate	35.0%
CC (Chronic HCV)	32.0%
Based on table 99, page 279 of the company's submission	

Intervention and comparator in the model

5.9 Patients received treatment in the first year in the model. The interventions included in the economic model were 3D with or without ribavirin for GT1 and 2D with ribavarin for GT4 HCV according to the recommendation in the summary of product characteristic (see Table 3). The company compared 3D and 2D regimens with the comparators as specified in the company's decision problem, sofosbuvir+ PR, telaprevir+ PR, boceprevir+ PR and PR (see Table 2). The 3D, 2D and comparator regimens were modelled in line with their respective marketing authorisations. For the comparison with peginterferon, the company used both peginterferon alfa-2a (Pegasys, Roche) and peginterferon alfa-2b (ViraferonPeg, Merck, Sharp and Dohme) weighted by market share. The company estimated the average treatment durations using data on discontinuations reported in the trials for the 3D and 2D

regimens as well as in the trials for the comparator regimens. For further details see tables 113-114, page 359-360 of the company's submission.

Modelling of clinical effectiveness

5.10 The clinical effectiveness was modelled as the probability of moving to a recovery state which was based on the SVR reported in the clinical trials. The company included estimates of effectiveness from separate trials without any statistical adjustments. Where the clinical efficacy data were available from more than 1 trial, the company used results driven by simple pooling of the number of responders and total number of patients. The SVRs for 3D, 2D and the comparator regimens used in the model and their sources are summarised in tables 33-36, pages 89-93 of the ERG report.

Adverse events

5.11 The adverse events included in the model were: anaemia, neutropenia, thrombocytopenia, rash and depression. The incidences of adverse events were based on the adverse events reported in the same trials used to inform clinical effectiveness. The company's submission is not explicit regarding the grade of included adverse events included in the model. For further details see table 38, page 97 of the ERG report.

Utility values

5.12 For the health states in the model, the company used utility values obtained from EQ-5D collected in the UK Mild Hepatitis C trial and valued using the UK general population tariff. Health state utility values used in the model are provided in Table 15.

Table 15 Health state utility values

Health-state	Utility	Source
Mild HCV	0.77	Wright et al 2006
Moderate HCV	0.66	Wright et al 2006
Compensated cirrhosis	0.55	Wright et al 2006
Recovered (no HCV, history of mild fibrosis)	0.82	Calculated – add 0.05 to utility for mild HCV
Recovered (no HCV, history of moderate fibrosis)	0.71	Calculated – add 0.05 to utility for moderate HCV
Recovered (no HCV, history of compensated cirrhosis)	0.60	Calculated – add 0.05 to utility for CC
Decompensated cirrhosis	0.45	Wright et al 2006
Hepatocellular carcinoma	0.45	Wright et al 2006
Liver transplant	0.45	Wright et al 2006
Post-liver transplant	0.67	Wright et al 2006
From table 39 (page 99) of the ERG report.		

5.13 The utility differences associated with the treatment were also accounted for in the model. On-treatment utility decrements or gains were applied during the first year (first cycle) of the model. To estimate on-treatment utility difference for the 3D and 2D regimens, the company calculated the difference in the EQ-5D-3L score at the end-of-treatment from baseline. EQ-5D-3L scores were calculated using UK crosswalk from the EQ-5D-5L collected in the trials for the 3D and 2D regimens (see section 7.4.3 of the company's submission). On-treatment utility deference for 3D and 2D regimens ranged from a decrement of [redacted] to a utility gain of [redacted]. The utility decrement associated with the comparator treatments were sourced from other NICE technology appraisals and ranged from a decrement of 0.154 (for telaprevir+ PR in treatment experienced patients) to a utility gain of 0.010 (for boceprevir +PR in treatment

experienced patients). For further details see table 101, page 285 of the company's submission.

Resource use and costs

5.14 The company included 2 categories of resource use in the model that is; health states costs and treatment costs. The health state costs were associated with management of progressive liver disease (in patients who do not respond to treatment) and costs associated with post-treatment surveillance following treatment cessation and achievement of SVR. The company's estimation of resource use for health states were based on 2 sources;

- A retrospective chart review of patients with CHC that reported resource use in CHC patients according to their response to treatment (SVR or Non-SVR) conducted in the East Midlands region of the UK (Backx et al., 2014). The company used resource use reported by Backx et al. to estimate costs for all 3 recovered health states and 2 disease state moderate fibrosis and compensated cirrhosis.

- The cost for remaining health states that is; mild fibrosis and 3 more advanced disease stages namely decompensated cirrhosis, hepatocellular carcinoma and liver transplant were based on the models used in NICE technology appraisals 106 and 200. The cost were updated to current values using the PSSRU pay and prices inflation index. The costs used in the model are provided in Table 16.

Table 16 Health state costs

Health state	Cost (2012/13)	Source
Mild (Chronic HCV)	£160	Hartwell 2011
Moderate (Chronic HCV)	£589	Backx 2014
CC (Chronic HCV)	£914	Backx 2014
Recovered, no HCV, history of mild fibrosis	£58	Backx 2014
Recovered, no HCV, history of moderate fibrosis	£58	Backx 2014

Recovered, no HCV, history of severe fibrosis (CC)	£586	Backx 2014
DCC	£12,333	Hartwell 2011
HCC (first year)	£10,990	Hartwell 2011
HCC (subsequent year)	£10,990	Hartwell 2011
Liver transplant (first year)	£49,749	Hartwell 2011
Liver transplant (subsequent)	£1,873	Hartwell 2011
Based on table 123 (page 386) of the company's submission.		

5.15 Treatment related costs included drug acquisition costs, costs associated with on-treatment monitoring for response and adverse events to treatment. Total drug acquisition cost for 3D, 2D and the comparator regimens used in the model has been summarised by the ERG (see table 42 of the ERG report). For further details, see tables 120 (page 379), 121 (page 384) and 122 (page 386) of the company's submission.

ERG comments

5.16 The ERG commented that the company did not discuss the comparability of the modelled population taken from the clinical audit used in the model for previous NICE technology appraisals and the population in the clinical trials (in terms of baseline demographic characteristics) informing the clinical effectiveness and safety of treatments.

5.17 The ERG did not agree with the company's suggestion that for patients with GT1 CHC, telaprevir+ PR is the main comparator; the clinical advice to the ERG suggested that boceprevir would be used as frequently as telaprevir in GT1 patients. The ERG agreed that PR dual therapy would not be used in GT1 patients unless there was a reason not to include a protease inhibitor (telaprevir and boceprevir) in the treatment regimen.

5.18 The ERG noted that the company used the same SVR estimates for both interferon-eligible and interferon-ineligible populations without giving any justification.

5.19 The ERG was concerned that method used by the company to estimate average duration of the treatments (see section 5.9) may not fully capture treatment-futility stopping rules for peginterferon based regimens or response-guided regimen of telaprevir and boceprevir.

5.20 The ERG noted that the SVR for PR in the SPRINT-2 trial, from which the SVR for boceprevir+ PR used in the model was taken, was lower than that SVR for PR used in the model. The ERG thought it would underestimate the effectiveness of boceprevir +PR relative to PR in the model. The ERG conducted an exploratory analysis after adjusting SVR for boceprevir (see ERG's exploratory scenario 'c' section 5.42).

5.21 The ERG commented that the model outcomes should be interpreted with caution because the clinical effectiveness data (SVRs) was sourced from different trials without any statistical adjustment to account for heterogeneity between trials. The ERG thought that an alternative approach to the analysis could have been a threshold analysis of 3D and 2D regimens in a model based on a consistent evidence network.

5.22 The ERG questioned the rationale for using different on-treatment utility decrement/gain for 3D and 2D regimens stratified by fibrosis stage and treatment history for each genotype sub-group, as reported in Table 110 (page 354-355) and in Table 111 (page 356) of the company's submission. The ERG commented that the company did not provide any discussion on the clinical interpretation or statistical interaction of the different on-treatment utility gain/decrement identified in the trials. The ERG was concerned that the modelling of 'on-treatment utility difference', which was supposed to capture the disutility associated with adverse events showed a utility gain instead, for a number of groups (meaning patients are better on-treatment than off it). The ERG commented that it could double-count the utility benefit associated with SVR which was already captured by the change in the health state from diseased to recovery.

5.23 The ERG noted that the company did not include simeprevir as a comparator for any genotype because of the lack of suitable publicly available data. It commented that data from a mixed treatment comparison for the Q80K negative population undertaken for the NICE technology appraisal of simeprevir (TA 331), could have allowed a comparison with simeprevir. For further details see pages 91-92 of the ERG report. The ERG conducted an exploratory analysis including simeprevir as a comparator (see analysis 'd' in section 5.42).

5.24 The ERG also questioned the method used for on-treatment utility difference calculation. The calculation was based on the patient responses at end of treatment which was likely to miss patients who had discontinued treatment due adverse effects of treatment. The ERG however acknowledged that this is less likely to be a significant problem here, because only few patients discontinued treatment in the trials due to adverse effects.

5.25 The ERG commented that the company provided limited information on the model validation exercises. The ERG noted that the company did not compare the results obtained for comparator technologies from its model with the results identified in the literature or previous NICE technology appraisals.

5.26 The ERG noted that to populate the model, the company applied a number of imputations to the clinical data for example SVR for specific patient groups or different stages of fibrosis was imputed from trial results based on many assumptions and sometimes was based on very small sub-groups of trial populations. The ERG was concerned that the model did not account of the additional uncertainty arising from these imputations.

Company's base-case results and subgroup analyses

5.27 The company presented base-case results for following patient population separately:

- GT1, treatment-naïve, interferon eligible patients,
- GT1, treatment-experienced (overall) interferon eligible patients,
- GT4, treatment-naïve, interferon-eligible patients (non-cirrhotic only),
- GT4, treatment-experienced (overall) interferon eligible patients (non-cirrhotic only).

5.28 The company presented fully incremental analyses including all comparators specified in its decision problem (see Table 17) as well as pair-wise analyses comparing 3D and 2D regimens with one comparator at a time (see Table 18)

5.29 The company also presented results for the interferon ineligible population comparing 3D and 2D with best supportive care (see Table 19)

Company's subgroup analyses

5.30 The company presented results for subtypes of GT1 CHC (1a and 1b) separately as subgroup analyses. The results are summarised in Table 20. For further details, see table 143-146, page 439-440 of the company's submission.

5.31 For treatment experienced patients, the company presented subgroups based on the response to previous treatment (non-response, partial response and relapse). See Table 21 for a summary of the results and tables 147-149, pages 440-441 of the company submission for further details.

ERG exploratory analyses: Base case analyses by cirrhosis status

5.32 In an addendum to the ERG report, the ERG provided cost effectiveness estimates separately for patients with and without cirrhosis. A summary of the results are provided in Table 22. As the 2D regimen was not

studied in patients GT4 with cirrhosis SVR was assumed to be 97% as reported for 24 weeks regimen of 2D in patients with GT1b CHC in the EPAR.

Table 17 Company's base-case results (fully incremental analyses)

Regimen	Total costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	ICER (£/QALY)
GT1, treatment-naïve, interferon eligible patients					
PR	22,872	13.72	NA	NA	NA
Boceprevir + PR	32,147	14.22	9,275	0.50	Extended dominance
Telaprevir + PR	35,887	14.55	13,014	0.83	Extended dominance
3D Regimen	**43,624**	**15.21**	**20,752**	**1.50**	**13,864**
Sofosbuvir + PR	44,337	15.01	21,465	1.29	Dominated
GT1, treatment-experienced (overall) interferon eligible patients					
PR	30,128	11.07	NA	NA	NA
Telaprevir + PR	42,646	12.10	12,518	1.04	Extended dominance
3D Regimen	**51,882**	**13.19**	**21,754**	**2.12**	**10,258**
GT4, treatment-naïve, interferon-eligible patients (non-cirrhotic only)					
PR	19,286	15.00	NA	NA	NA
2D Regimen	**36,490**	**15.84**	**17,204**	**0.85**	**20,351**
Sofosbuvir + PR	41,237	15.81	21,951	0.81	Dominated
GT4, treatment-experienced (overall) interferon eligible patients (non-cirrhotic only)					
No treatment	16,186	12.58	NA	NA	NA
2D Regimen	**36,536**	**14.84**	**20,350**	**2.27**	**8,977**
Based on the table 137- 140 of the company's submission (page 408-409)					

Table 18 Company's pairwise analyses of 3D/2D regimen compared with each comparator: (ICER:£/QALY)

Population	3D/2D regimen versus SOF + PR	3D/2D regimen versus TPR + PR	3D/2D regimen versus PR	3D/2D regimen versus BOC + PR	3D/2D regimen versus No Treatment
GT1, treatment-naïve (3D)	Dominant	11,677	13,864	11,572	NA
GT1, treatment-experienced (overall) (3D)	TBD	8,507	10,258	TBD	NA
GT4, treatment-naïve (non-cirrhotics only) (2D)	Dominant	NA	20,351	NA	NA
GT4 treatment experienced, non-cirrhotic	NA	NA	NA	NA	8,977

NA, not applicable; TBD, to be determined because cannot be assessed with current available data, based on the table 141 of the company's submission (page 409)

Table 19 Company's cost-effectiveness results in interferon ineligible patients

Population	Intervention		Best supportive care		Incremental		ICER (£/QALY)
	Cost (£)	QALY	Cost (£)	QALY	Costs (£)	QALY	
GT1, treatment-naïve (3D)	43,624	15.21	19,788	12.70	23,837	2.51	9,498
GT1, treatment-experienced (overall) (3D)	51,882	13.19	24,245	10.80	27,637	2.38	11,597
GT4, treatment-naïve (non-cirrhotics only) (2D)	36,490	15.84	17,230	13.31	19,260	2.53	7,614
Based on table 150-152 of the company's submission (page 441 of the company's submission)							

Table 20 Company's subgroups analysis based on subtypes of GT1 (1a and 1b)

Regimen	Total costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	ICER (£/QALY)
GT1a, treatment-naïve, interferon eligible patients					
PR	23,305	13.64	NA	NA	NA
Boceprevir + PR	32,905	14.09	9,601	0.45	Extended dominance
Telaprevir + PR	36,378	14.47	13,073	0.82	Extended dominance
Sofosbuvir + PR	44,064	15.06	20,760	1.41	Extended dominance
3D Regimen	**45,110**	**15.18**	**21,805**	**1.54**	**14,199**
GT1b, treatment-naïve, interferon eligible patients					
PR	22,190	13.84	NA	NA	NA
Boceprevir + PR	31,832	14.28	9,642	0.44	Extended dominance
Telaprevir + PR	35,210	14.67	13,020	0.83	Extended dominance
3D Regimen	**40,348**	**15.29**	**18,159**	**1.46**	**12,453**
Sofosbuvir + PR	45,516	14.80	23,327	0.97	Dominated
GT1a, treatment-experienced (overall) interferon eligible patients					
PR	29,458	11.16	NA	NA	NA
Telaprevir + PR	43,559	11.96	£14,101	0.80	Extended dominance
3D Regimen	**55,552**	**13.17**	**£26,093**	**2.01**	**12,978**
GT1b, treatment-experienced (overall) interferon eligible patients					
PR	30,738	10.98	NA	NA	NA
Telaprevir + PR	41,579	12.26	10,841	1.28	Extended dominance
3D Regimen	**43,790**	**13.22**	**13,052**	**2.24**	**5,828**
Based on the table 143-146 of the company's submission (page 439-440)					

Table 21Company's subgroup analysis for treatment experienced patients with GT1 CHC based on prior response

Regimen	Total costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	ICER (£/QALY)
GT1, treatment-experienced, **null responders** patients					
PR	31,630	10.82	NA	NA	NA
Telaprevir + PR	47,701	11.29	16,072	0.47	Extended dominance
3D Regimen	**52,089**	**13.16**	**20,459**	**2.34**	**8,755**
GT1, treatment-experienced **partial responders** patients					
PR	29,486	11.11	NA	NA	NA
Telaprevir + PR	43,041	12.10	13,555	1.00	Extended dominance
Boceprevir + PR	47,403	11.48	17,917	0.38	Extended dominance
3D Regimen	**51,770**	**13.21**	**22,284**	**2.11**	**10,584**
GT1, treatment-experienced **prior relapsers** patients					
PR	29,483	11.22	NA	NA	NA
Telaprevir + PR	38,558	12.71	9,075	1.49	£6,091
Boceprevir + PR	42,763	12.18	13,280	0.96	Dominated
3D Regimen	**51,811**	**13.19**	**22,328**	**1.97**	**27,601**
Based on the table 147-149 of the company's submission (page 440-441)					

Table 22 ERG'S exploratory analyses: ICERs (£/QALY) for patients with or without cirrhosis

Population	Naïve		Experience	
	Non-cirrhotic	Cirrhotic	Non-cirrhotic	Cirrhotic
GT1 (combined 1a and 1b)*	13,306	36,139	8,581	13,060
GT1a	12,949	75,360	9,589	18,539
GT1b	13,515	5,924	7,401	3,087
GT4	20,351	36,472	8,977	15,868
*68.8% Gt1a + 31.2%GT1b as in the base-case analyses Based on the tables 2,4,6,8,10,12,13 and 14 of the addendum to the ERG report				

Company's sensitivity analyses

Deterministic sensitivity analyses

5.33 The company conducted deterministic sensitivity analysis by varying various parameters used in the model. The parameters varied were related to the transition probabilities of the disease progression, health state costs, health state utility values, costs of treating adverse events as well clinical effectiveness of the treatments (both intervention and the comparator). For further details of the parameters varied and the values used in the sensitivity analyses, see table 128, page 394 of the company's submission. The company presented results of sensitivity analyses in the form of tornado diagrams (see figures 29-37, pages 411 to 419 of the company's submission). The results of sensitivity analyses showed that the ICERs were most sensitive to the health state utility values (particularly for the recovered health state with history of mild or moderate fibrosis).

Probabilistic sensitivity analyses

5.34 The company conducted probabilistic sensitivity analyses for each of the 4 modelled patient populations defined by genotype and prior treatment history as considered in the base case. The company reported the variables and distributions used in the probabilistic analyses (see table 129, page 396 of the company's submission). The company ran 500 iterations for each analysis and presented results graphically in the form of cost-effectiveness acceptability curves (see figures 38-41, page 420-422 of the company's submission). The company commented that:

- For GT1, treatment naïve patients, the 3D regimen became the optimal treatment option only if the willingness to pay is £15,000 or more per QALY gained.
- For GT1, treatment-experienced patients, the 3D regimen became the optimal treatment option only if the willingness to pay is £13,000 or more per QALY gained.
- For GT4, treatment-naïve patients, the probability of 2D regimen being cost-effective at a willingness to pay threshold of £23,000 per QALY gained was more than 50%.
- For GT4, treatment experienced patients, the probability of 2D regimen being cost-effective at a willingness to pay threshold of £18,000 per QALY gained was 100%.

ERG comments

5.35 The ERG commented that some of the parameters in the company's deterministic sensitivity analyses were varied by an arbitrary range without providing any justification, for example utility value was varied by 20% and costs were varied by 50%. The ERG also questioned the company's method of calculating distributions around SVR and adverse event and commented that for SVR using the upper and lower limit of beta distribution would have been preferable.

5.36 The ERG re-ran the probabilistic sensitivity analyses and reported the mean costs, QALYs and compared the probabilistic results with the deterministic results (see table 44-49, page 11-113 of the ERG report). The probabilistic results were consistent with the deterministic results for all of the 4 patient groups.

5.37 The ERG was concerned with the calculation of variability around SVR for patients with mild and moderate fibrosis for the probabilistic analyses. The ERG commented that the model applied standard error of the SVR of the overall combined population, to the SVRs for patients with different fibrosis state underestimating the uncertainty in the probabilistic sensitivity analyses. The ERG re-ran probabilistic sensitivity analyses using unpublished data from the clinical study reports for SVRs in patients with mild and moderate fibrosis. The result showed minimal impact on the results (see scenario 'b' of the ERG's exploratory analyses).

5.38 The ERG commented that uncertainty associated with the treatment effects captured in the probabilistic sensitivity analyses were the statistical uncertainty in the SVRs and adverse event rate. It noted that the model did not make any allowance for the methodological uncertainty arising from unadjusted indirect comparisons of alternative treatments.

Company's scenario analyses

5.39 The company also presented results for 21 different scenarios. The company listed all the scenarios on page 422 of the company's submission. The description of variables changed in the scenarios is detailed in the table 125 (page 389) of the company's submission. The company presented the results of scenario analyses in the tabulated forms (see table 142, page 423-432 of the company's submission).

5.40 All scenarios, except 1 (the company's scenario no. 16), were conducted for patients with GT1 CHC and results were presented separately for

treatment naïve and experienced patients. The company did not report fully incremental ICERs for 3D and other comparator regimens in the scenario analyses. All ICERs reported in the scenario analyses were pair-wise comparison with PR regimen. The scenarios and results are summarised in Table 23. Change in the discount rate, age at baseline, time horizon and proportion of patient with mild fibrosis as well as inclusion of indirect cost have substantial impact on the ICERs.

ERG comments

5.41 The ERG commented that results of scenario analyses (presented in a total of 39 tables) were difficult to interpret. The ERG would have preferred these analyses presented graphically or the company indicated some form of priority for the analyses.

Table 23 Company's scenario analyses

Scenario No.	Description of change	Base-case value	Naïve	Experienced
For GT1, ICERs compared with PR				
Base-case analysis			*£13,864*	*£10,258*
1	100% patients with mild fibrosis	46%	£19,788	£13,583
2	100% patients with compensated cirrhosis	10% for naïve 32% for experienced	£17,350	£13,060
3	Age at baseline 35 years	40 year	£12,396	£8,024
4	Age at baseline 55 years		£22,012	£14,539
5	65% Male	70%	£13,805	£10,206
6	75% Male		£13,923	£10,310
7	50% with GT1a subtype	68.8%	£13,076	£9,175
8	Transitional probabilities of disease progression from Grishchenko et al. (2009)	From Shepherd et al. (2007)	£14,889	£10,861
9	Include Indirect Costs	Not included	£1,413	Dominant (less costly and more

Scenario No.	Description of change	Base-case value	Naïve	Experienced
				effective than PR)
10	Discount rates 0%	3.5%	£3,741	£2,637
11	Discount Rates 6%		£24,225	£18,037
12	Time horizon 30 years	70	£20,097	£13,525
13	Therapy duration (no dropouts)	Trial-based discontinuation	£12,351	£8,873
14	Alternative SVR for comparator from Hadzyannis et al. (2004) 56.0% for mild, 56.0 for moderate and 38.0% for compensated cirrhosis	From ADVANCE trial (45.6% for mild, 43.5% for moderate and 33.3 for compensated cirrhosis	£18,363	Not reported
15	Alternative SVR for comparator from McHutchinson et al. (2009) 43.6% for mild, 43.6% for moderate and 23.6% for compensated cirrhosis		£13,246	Not reported
16	See below for scenario analysis in GT4			
17	SVR for 3D regimen stratified for mild and moderate fibrosis	SVR not stratified by mild/moderate fibrosis	£14,048	Not reported
18	Alternative sofosbuvir +PR duration in patients with compensated cirrhosis (20% for 12 week, 80% for 24 weeks)	100% for 12 weeks	£13,864	Not reported
19	4.56% increase in utility values of recovered states from corresponding disease state (Vera Llonch, 2013)	0.05 absolute increase from corresponding disease sate	£15,607	£11,659
20	Disease-state utility values based on EQ-5D UK crosswalk from 3D trials	Based on previous model	£16,875	£13,076
21	12 weeks of 3D+R in GT1a cirrhotic patients with favorable baseline laboratory values	24 weeks for all patients with cirrhosis	£12,762	£8,301

Scenario No.	Description of change	Base-case value	Naïve	Experienced
	([redacted] were treated for 12 weeks)			
For GT 4 non-cirrhotic, ICERs compared with PR in treatment naïve, and with no treatment for treatment experienced				
Base-case analysis			*£20,351*	*£8,977*
16	SVR for PR 61.3% from Yee et al.(2014)	70.6% from Kamal et al. (2011)	£14,691	£8,977
PR; peginterferon and ribavirin, based on table 125 (page 389) table 142 (page 423-432) of the company's submission				

ERG's exploratory analyses

5.42 The ERG conducted a number of exploratory analyses which included:

a. Using the SVR data from head-to-head comparisons of 3D and telaprevir +PR (MALACHITE I and MALACHITE II trials),

b. Re-running the probabilistic sensitivity analyses using fibrosis stage-specific SVRs (mild and moderate fibrosis stages) from 3D trials instead of values pooled across fibrosis stages (see above section 5.35),

c. Re-running the base case analysis adjusting effectiveness of boceprevir +PR,

d. re-running the base case analysis including simeprevir+ PR,

e. re-running the base case analysis (for GT1 treatment-naive non-cirrhotic patients) using an adjusted indirect comparison – to include PR and boceprevir +PR in addition to 3D and telaprevir +PR,

f. conduct a threshold analysis on the relative effectiveness (SVR) for 3D and 2D,

g. present a scenario using an alternative estimate of the risk of HCC for those patients who underwent SVR from the compensated cirrhosis health state,

h. present a scenario using an alternative estimate for the risk of HCC for those in the compensated cirrhosis health state,

i. combine scenarios g and h.

5.43 The results of the ERG's exploratory analyses are provided in Table 24.

Table 24 ERG's exploratory analyses

ERG's Scenario	Description	Patient group	ERG's exploratory ICER (£)	Corresponding ICER from the company's analyses (£)	Reference to ERG report
a	SVR data from head-to-head comparisons of 3D and telaprevir +PR (MALACHITE I and MALACHITE II trials) for non-cirrhotics only	GT1 naïve	9,212 (compared with telaprevir +PR)	9,521 (compared with telaprevir +PR)*	Table 50
		GT1 experienced	4,036 (compared with telaprevir +PR)	4,287 (compared with telaprevir +PR)*	Table 51
b	Re-running the PSA using fibrosis stage-specific SVRs (mild and moderate fibrosis stages) from 3D trials instead of values pooled across fibrosis stages (see above section 5.37)	Minimal impact on the probabilistic results on using fibrosis stage-specific SVRs from 3D trials in the PSA instead of pooled estimates			Page 118
c	Re-running the base case analysis adjusting effectiveness of boceprevir +PR	GT1 naïve	15,206 (compared with boceprevir +PR)	13,864 (compared with PR, boceprevir was externally dominated)	Table 55
d	Re-running the base case analysis including simeprevir+ PR	GT1 naïve	14,010 (compared with simeprevir)	13,864 (compared with PR)	Table 56
e	Re-running the base case analysis (for GT1 treatment-naive non-cirrhotic patients) using an adjusted indirect comparison – to include PR and boceprevir +PR in addition to 3D and telaprevir +PR	GT1 naïve	15,477 (compared with boceprevir +PR	13,297 (compared with PR, boceprevir was externally dominated)	Table 58
f	threshold analysis on the relative effectiveness (SVR) for 3D and 2D	Threshold analysis showed that if the effectiveness of 3D is reduced to • 92% of the effectiveness used in the base-case, the ICER will be £109,535 per QALY gained			Table 59 and Figure 3

ERG's Scenario	Description	Patient group	ERG's exploratory ICER (£)	Corresponding ICER from the company's analyses (£)	Reference to ERG report
		• below 92%, 3D would be dominated by sofosbuvir+ PR			
g	alternative estimate of the risk of HCC for those patients who underwent SVR from the compensated cirrhosis health state; from Bruno et al. (2007)	GT1 naïve	13,421 (compared with PR)	13,864 (compared with PR)	Table 60
		GT1 experienced	9,390 (compared with PR)	10,258 (compared with PR)	Table 60
h	alternative estimate for the risk of HCC for those in the compensated cirrhosis health state; from Bruno et al. (2007)	GT1 naïve	13,390 (compared with PR)	13,864 (compared with PR)	Table 61
		GT1 experienced	9,777 (compared with PR)	10,258 (compared with PR)	Table 61
i	combine scenarios g and h	GT1 naïve	13,390 (compared with PR)	13,864 (compared with PR)	Table 62
		GT1 experienced	8,991 (compared with PR)	10,258 (compared with PR)	Table 62
* calculated by the ERG for patients without cirrhosis only using base-case assumption					

Innovation

5.44 Ombitasvir/paritaprevir/ritonavir with or without dasabuvir was considered to be innovative because it is:

- an all-oral regimen.
  - easy to administer,
  - requires less support from healthcare professionals,
  - potential to improve productivity of the patients,
- an interferon-free regimen.
  - free from adverse effects of interferon,
  - valuable for those not suitable for interferon based therapies,
- more effective than current standard of care.
  - shorter duration of treatment,
  - potential to reduce onward transmission (not likely to be captured in the QALY calculation),
  - may reduce the demand for liver transplant and improve waiting list (not likely to be captured in the QALY calculation).

6 Equality issues

6.1 During consultation on the draft scope the company commented that the impact of age on the ICER should be excluded from consideration because increased background mortality is found to negatively impact the ICER. And at the scoping workshop 1 patient expert stated that in clinical practice there may be a reluctance to treat people who use intravenous drugs with new treatments for hepatitis C due to fear of drug interactions and it may be a potential barrier to access. It was also

suggested that a positive statement from NICE about not excluding patients who use intravenous drugs for this combination therapy will be helpful.

6.2 The preliminary view at the scoping workshop on impact of age on the ICER was that it was not particularly an equality issue. It was considered an issue related to the economic evaluation of the technology and will be deliberated by the Committee. Attendees of the scoping workshop agreed that any guidance should ensure it does not exclude the patient groups who use intravenous drugs unless there is explicit evidence on the risk of harm due to drug interactions.

6.3 The company identified following equality issues (see the company's submission page 49-50):

- Ethnic minority groups (equality legislation) are disproportionately affected by GT4 CHC. Therefore, differential recommendations on the use of 3D or 2D for patients with GTs 1 and 4 CHC could potentially disadvantage and discriminate against people with family background of Middle East and Africa.

- People with HIV co-infection (equality legislation): People with HIV co-infection may be classified as disabled under disability discrimination legislation. Therefore, as evidence is presented to show the efficacy of 3D does not differ in patients with HIV co-infection, recommendations on the use of 3D or 2D should not differ for patients with or without HIV co-infection.

- Prison populations and homeless people (health inequalities): Effective CHC treatments for these patients have potential for reducing health inequalities given that these groups have a higher prevalence of CHC infection.

- Patients with cirrhosis (type of equality issue not specified): Differential recommendations should not be made for patients

with and without cirrhosis, as some patients may be misclassified as having a Metavir score of F3 when they have a score of F4.

7 Authors

Dr Anwar Jilani

Technical Lead

Nicola Hay

Technical Adviser

with input from the Lead Team (Dr Mohit Sharma, Dr Aomesh Bhatt and Malcolm Oswald).

Appendix A: Clinical efficacy section of the draft European public assessment report

The section 2.5 of the European public assessment report (pages 87–117) details the clinical efficacy of ombitasvir/paritaprevir/ritonavir in chronic hepatitis C.

Sections 2.5 and 2.6 of the European public assessment report (pages 61–84) detail the clinical efficacy of dasabuvir in chronic hepatitis C.

Appendix B: NICE technology appraisal No. 300 'Sofosbuvir for treating chronic hepatitis C'

Table 1 Summary of recommendations

	Sofosbuvir in combination with peginterferon alfa and ribavirin		**Sofosbuvir in combination with ribavirin**	
Genotype	**Treatment history**	**Recommendation**	**Treatment history**	**Recommendation**
Adults with genotype 1 HCV	All	Recommended	All	Not recommended
Adults with genotype 2 HCV	All	Not licensed for this population	Treatment- naive	Only recommended for people who are intolerant to or ineligible for interferon
			Treatment- experienced	Recommended
Adults with genotype 3 HCV	Treatment-naive	Only recommended for people with cirrhosis	Treatment-naive	Only recommended for people with cirrhosis who are intolerant to or ineligible for interferon
	Treatment-experienced	Recommended	Treatment-experienced	Only recommended for people with cirrhosis who are intolerant to or ineligible for interferon
Adults with genotype 4, 5, or 6 HCV	All	Only recommended for people with cirrhosis	All	Not recommended

HCV – hepatitis C virus
Treatment-naive – the person has not had treatment for chronic hepatitis C
Treatment-experienced – the person's hepatitis C has not adequately responded to interferon-based treatment
Interferon unsuitable – the person is intolerant to or ineligible for interferon