NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Viekirax® + Exviera® (Ombitasvir/paritaprevir/ritonavir and dasabuvir (3D)) for chronic hepatitis C genotype 1

Viekirax® Ombitasvir/paritaprevir/ritonavir (2D) for chronic hepatitis C genotype 4

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Abbreviations

AE	Adverse Event
AFP	Alfa-fetoprotein
ALT	Alanine aminotransferase
AST	Aspartate transaminase
BIM	Budget Impact Model
BMI	Body Mass Index
BNF	British National Formulary
BOC	Boceprevir
CEA	Cost Effectiveness Analysis
CHC	Chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CUA	Cost Utility Analysis
DAA	Directly acting antiviral
DRESS	Drug Rash With Eosinophilia and Systemic Symptoms
DSA	Deterministic Sensitivity Analysis
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
EASL	European Association For The Study Of The Liver
ECG	Electrocardiogram
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency
EMBASE	Excerpta Medica Database
EPAR	European Public Assessment Report
EPO	Erythropoietin
EQ-5D-3L	EuroQol-5 Dimension 3-Level
EQ-5D-5L	EuroQol-5 Dimension 5-Level
EOTR	End of Treatment Response
ERG	Evidence Review Group
FBC	Full Blood Count
FDA	Food and Drugs Administration
GT	Genotype
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV-1	Human immunodeficiency virus
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
IDU	Intravenous Drug User
IFN	Interferon
INMB	Incremental Net Monetary Benefit
KOL	Key Opinion Leader
PegIFN	Pegylated interferon
PegIFN/RBV	Pegylated interferon and ribavirin
PR	Pegylated interferon and ribavirin
RBV	Ribavirin
SOF	Sofosbuvir
SIM	Simeprevir
TPV	Telaprevir

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Executive summary

Introduction

Burden of disease

Liver disease is the 5th biggest cause of mortality in England after cancer, heart disease, stroke and respiratory disease. Hepatitis C is a serious infectious disease caused by the blood borne hepatitis C virus (HCV) and is the most common cause of chronic liver disease and cirrhosis; it is also the most common indication for liver transplantation in most of Europe. Chronic HCV infection is associated with significant morbidity, mortality and economic burden.

Around 75% of people infected with hepatitis C will develop chronic infection. Chronic infection with hepatitis C, if left untreated or if unsuccessfully treated, can cause cirrhosis and liver cancer in a significant proportion of patients. Once cirrhosis has developed, hepatic decompensation and other potentially fatal complications can occur and liver transplantation may be required. However, before cirrhosis develops, hepatitis C infection can cause fatigue with a resultant negative impact on quality of life. In addition, HCV has also been found to replicate in sites outside the liver, including bone marrow, the central nervous system, endocrine glands, lymphatic tissue and skin cells. This can result in a host of extra-hepatic manifestations, including autoimmune disease, skin reactions, renal injury and neuropathy; it is estimated that up to 76% of patients with chronic HCV experience at least one such manifestation.4 These extra-hepatic manifestations contribute considerably to the overall disease burden in chronic HCV patients.

There are 6 different genotypes of hepatitis C. The most common genotypes in the UK (~90%) are Genotype 1 (GT1) and Genotype 3 (GT3). GT2, 4, 5, and 6 make up the rest of the remaining identified genotypes. More than 200,000 people in the UK are chronically infected with hepatitis C, with 160,000 of these estimated to be in England alone. Yet due to the asymptomatic nature of the infection in its early stages, many people are unaware they are infected with hepatitis C until the disease is severe.

In the UK only around 3% of the prevalent pool of people infected with hepatitis C are treated each year. This is attributable to a number of factors including the silent nature of the disease, a low diagnosis rate of approximately 50%, a lack of uniformity in the delivery of hospital care and unwillingness from many patients to undergo treatment. Historically, therapies for hepatitis C have only been effective in a proportion of those treated. As a result, mortality due to hepatitis C is increasing at a rapid rate in the UK.

The goal of hepatitis C treatment is viral eradication, measured by the achievement of a sustained virologic response (SVR). SVR is defined as non-detectable virus in the blood 12 or 24 weeks (SVR12 or SVR24) after a course of therapy is completed. Viral eradication prevents the progression of hepatitis C related liver fibrosis and associated complications such as HCC in the majority of cases and delivers ‘virologic cure’ for people infected with hepatitis C.

Studies have shown that patients who achieve an SVR are more than four times less likely to be hospitalised or to die from a liver-related cause than patients who fail to achieve an SVR.

Tackling this infection and the premature mortality that results has to be a core part of any programme to reduce such health inequalities and to improve health overall especially amongst the most marginalised groups of our society.

Public Health England publishes annual reports on Hepatitis C in the UK. The 2014 Report specifically and categorically recommends that four action areas should be implemented vigorously to achieve success in eradicating the disease. They are:

1. Prevention of new infections
2. Increasing awareness of infection
3. Increasing testing and diagnosis
4. Getting diagnosed individuals into treatment and care

Unmet need

Current NICE recommended treatment options for patients in England and Wales all involve the co-administration of Peg-interferon + ribavirin (PegIFN/RBV). Traditionally, patients with HCV genotype 1 received one of the protease inhibitors (telaprevir or boceprevir) in combination with PegIFN/RBV, or PegIFN/RBV alone. While these current treatment options are successful and provide a cure for some patients they are not successful in a substantial proportion. The current therapies are also associated with a range of limitations including long and complicated treatment regimens, intolerable side-effects and the development of treatment-resistant viral mutations all of which can lead to treatment failure. The introduction of newer therapies: simeprevir + PegIFN/RBV or sofosbuvir + PegIFN/RBV, are a welcome advantage to the arsenal of treatments for patients with chronic hepatitis C, but still require the co-administration of PegIFN/RBV. The limitations with current treatments, because of the side effects associated with PegIFN therapy, mean that the majority of diagnosed patients are without suitable treatment options. It is estimated that only 40% of HCV patients are considered eligible for treatment, hence there is a significant need for treatments which can be more widely used.

There is a clear medical need for new treatments which provide shorter, simpler, better tolerated and more effective regimens with a high likelihood of success. AbbVie's all-oral, interferon-free anti-viral combination thus has the potential to significantly improve patients' HRQoL by allowing greater numbers of patients, including those who are not eligible for or intolerant to the current regimens, to receive shorter, more efficacious and more tolerable therapy. With the increasing burden of chronic HCV the effective treatment of patients is essential in order to avoid progression of the disease and the associated complications, including excess mortality.

The Technology – 3D and 2D

AbbVie has developed two all oral, interferon-free direct acting antiviral regimens, the first for chronic hepatitis C genotype 1 (HCV GT1) and the second for chronic hepatitis C genotype 4 (HCV GT4). The HCV GT1 regimen is composed of ombitasvir/ paritaprevir/ ritonavir given in combination with dasabuvir. This HCV GT1 regimen is denoted as 3D in this submission document as it contains three direct acting antiviral therapies. For HCV GT4 ombitasvir/ paritaprevir/ ritonavir is given

without dasabuvir and is referred to as 2D as it contains two direct acting antiviral therapies. Ritonavir is included as a pharmacokinetic enhancer for paritaprevir.

Generic name:

- GT1 - ombitasvir/ paritaprevir/ ritonavir plus dasabuvir (3D)
- GT4 ombitasvir/ paritaprevir/ ritonavir (2D)

Brand name:

- GT1 – Viekirax + Exviera (3D)
- GT4 – Viekirax (2D)

The formulation, strength, pack size, anticipated frequency of any repeated courses of treatment and acquisition cost:

Viekirax is the brand name for the co-formulated tablet of ombitasvir 12.5mg/ paritaprevir 75mg/ ritonavir 50mg and is given as two tablets once daily. Exviera is the brand name for the dasabuvir 250mg tablet and is given twice daily. Viekirax packs contain 56 tablets and Exviera packs also contain 56 tablets to give 28 days' treatment. The acquisition cost of 3D for 28 days' supply is £11,666.76 and the cost of 2D for 28 days' supply is £10,733.33. Repeated courses are not anticipated given the high probability of achieving SVR with both 3D and 2D.

Regulatory status:

The 2D (Viekirax) and 3D (Viekirax + Exviera) regimens are being reviewed under the EMA's centralised procedure and positive opinion was granted in November 2014 with final marketing authorisation expected in January 2015.

Mechanism of action:

The 3D regimen combines three direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle. Ritonavir is not active against HCV. Ritonavir is a CYP3A inhibitor that increases the systemic exposure of the CYP3A substrate paritaprevir.

1. Ombitasvir is an inhibitor of HCV NS5A which is essential for viral replication.
2. Paritaprevir is an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication.
3. Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome.

Indication:

The regimens have the following indication:

Viekirax is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults

Exviera is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults (see Table 1 for licensed combinations and treatment duration).

Table 1: Recommended co-administered medicinal product(s) and treatment duration by patient population

Patient Population	Treatment*	Duration
Genotype 1b, without cirrhosis	3D	12 weeks
Genotype 1b, with compensated cirrhosis	3D + ribavirin	
Genotype 1a, without cirrhosis	3D + ribavirin	
Genotype 1a, with compensated cirrhosis	3D + ribavirin*	24 weeks
Genotype 4, without cirrhosis	2D + ribavirin	12 weeks
Genotype 4, with compensated cirrhosis	2D + ribavirin	24 weeks***
*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.		

Main comparators:

The main comparators for AbbVie's regimens are listed below. Note, where certain combinations are not recommended by NICE or where the evidence does not allow for a comparison, no analyses have been performed. Please see Section 2.7 and Section 7.3.1 for more detail.

HCV GT1:

- Telaprevir + PegIFN + RBV
- Boceprevir + PegIFN + RBV
- Simeprevir + PegIFN + RBV
- Sofosbuvir + PegIFN + RBV
- Best supportive care for PegIFN ineligible/intolerant patients

HCV GT4:

- PegIFN + RBV
- Sofosbuvir + PegIFN/RBV
- Simeprevir + PegIFN/RBV
- Best supportive care for PegIFN ineligible/intolerant patients

Clinical effectiveness

Summary of key clinical evidence

AbbVie's HCV regimens have been studied in an extensive clinical trial programme in over 2,000 chronic HCV patients as outlined in Table 24. Patient populations studied included HCV treatment-naïve and Peg-IFN + RBV treatment-experienced patients, and those with characteristics that have historically been associated with poor response to treatment such as cirrhosis, older age, and high baseline HCV viral loads. For HCV genotype 1, all the trials were powered to detect superiority of efficacy vs. historical control data from telaprevir + PegIFN/RBV – one of the listed comparators in the decision problem. The trials were designed in conjunction with

EMA and the US FDA where it was deemed that comparisons vs. historical cohorts of telaprevir were sufficient to demonstrate efficacy. AbbVie's clinical trials were therefore powered to detect inferiority and subsequent superiority vs. historical telaprevir SVR rates in similar populations. These designs were accepted due to the expectation of the high levels of efficacy for the 3D and 2D regimens based on phase 2 results which facilitated an accelerated phase III programme. A summary of the completed phase II/III trials used to support the EMA filing are listed below:

HCV GT1:

- SAPPHIRE-I (Feld et al) [31] – a double-blind, RCT evaluating the safety and efficacy of 3D + RBV in treatment naïve HCV GT1-infected adults without cirrhosis.

- SAPPHIRE-II (Zeuzem et al) [32] - a double-blind, RCT evaluating the safety and efficacy of 3D + RBV in PegIFN/RBV treatment experienced HCV GT1-infected adults without cirrhosis.

- TURQUOISE-II (Poordad et al) [33] - an open-label RCT evaluating the safety and efficacy of 3D + RBV in treatment naïve or treatment experienced patients with compensated cirrhosis.

- PEARL-II (Andreone et al) [34] – an open-label RCT evaluating the safety and efficacy of 3D with and without RBV in PegIFN/RBV treatment experienced HCV GT1b-infected adults without cirrhosis.

- PEARL-III (Ferenci et al) [35] - a double-blind, RCT evaluating the safety and efficacy of 3D with and without RBV in treatment naïve HCV GT1b-infected adults without cirrhosis.

- PEARL-IV (Ferenci et al) [35] - a double-blind, RCT evaluating the safety and efficacy of 3D with and without RBV in treatment naïve HCV GT1a-infected adults without cirrhosis.

- AVIATOR (Kowdley et al) [36] - an open-label, dose finding RCT evaluating the safety and efficacy of different combinations and treatment durations of 3D/2D +/- RBV in treatment naïve or treatment experienced HCV GT1 patients.

- M14-103 (CSR) [49] - an open-label, single arm, phase II study evaluating the safety and efficacy of 3D + RBV in HCV GT1 patients receiving opioid replacement therapy.

HCV GT4:

- PEARL-I (CSR) [39] – an open-label, randomised phase II trial evaluating 2D in HCV GT4 treatment naïve and treatment experienced patients without cirrhosis.

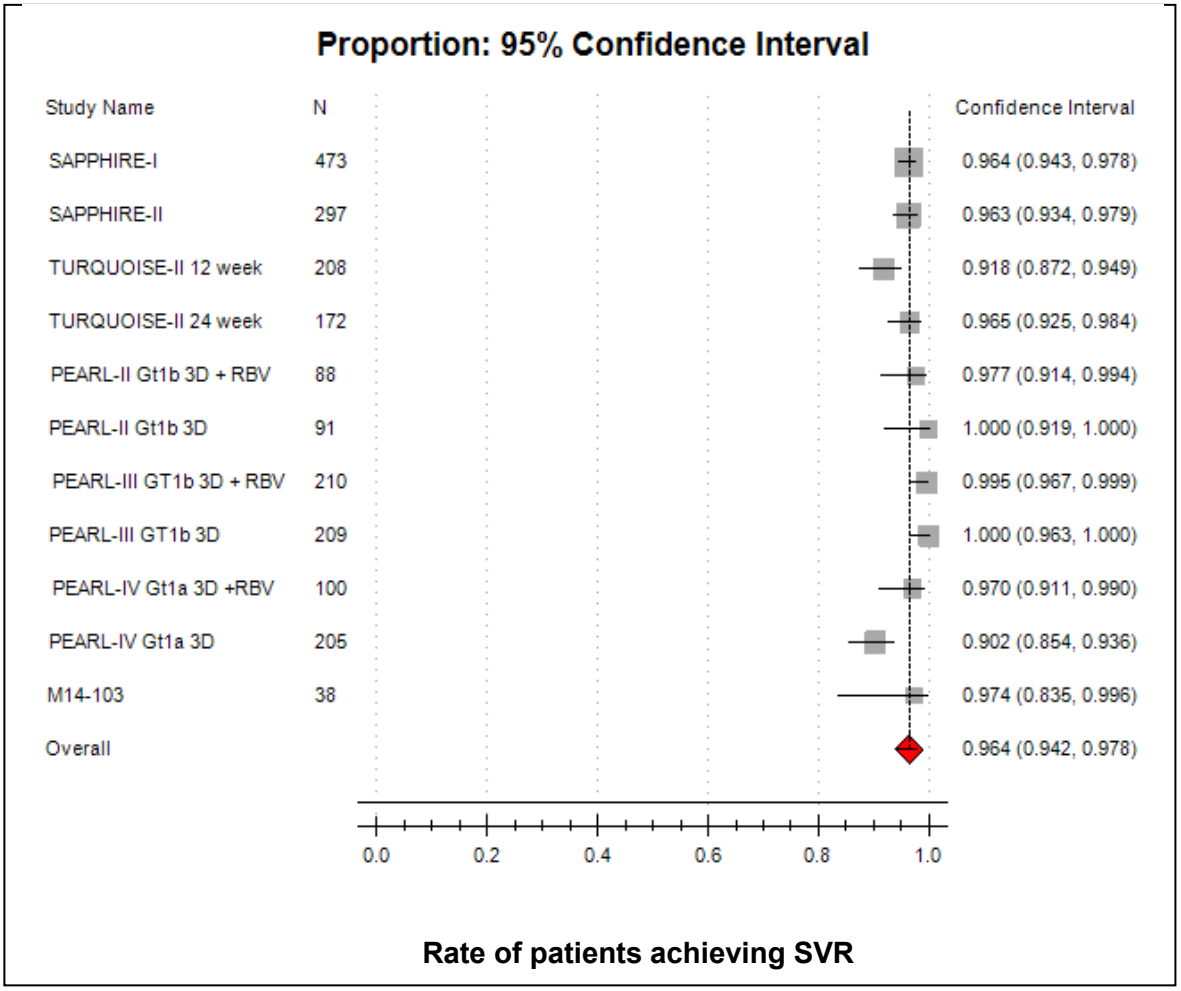
.

<u>Main results of the randomised controlled trials</u>**:**

In HCV GT1, treatment with 3D +/- RBV resulted in consistently high SVR rates across a broad population of patients including treatment naïve and treatment–

experienced patients, as well as difficult-to-treat patients such as those with cirrhosis; and in special populations, such as those with HIV co-infection or those who have had a liver transplant or are receiving opioid replacement therapy. Figure 1 summarises the SVR data across all the completed phase II/III trials used to support the regulatory filing to EMA, showing a pooled SVR of 96.4% for the overall HCV GT1 population.

Figure 1: Summary of SVR rates for 3D from the active arms in the HCV GT1 completed phase III clinical trials (and the phase II opioid study)



In HCV GT4, treatment with the licensed regimen of 2D resulted in a phenomenal 100% of treatment naïve and 100% treatment-experienced patients achieving SVR12.

The clinical benefits of being able to achieve such high SVR rates with 3D and 2D are twofold: firstly, the likelihood of onward transmission is considerably reduced, and secondly SVR12 results in regression of fibrosis and cirrhosis (i.e. liver function improves) and it is associated with a reduced rate of hepatic decompensation, a reduced risk for HCC and both a reduced rate of liver and non-liver related mortality.

In addition to the high probability of achieving SVR with AbbVie's regimens, the RCTs showed that there were very few side effects associated with 3D and 2D. Firstly, all the clinical trials collected patient reported outcome data looking at HRQoL – namely, the SF-36, EQ-5D-5L and the HCV-PRO. These data show that there was very little to no impact on HRQoL during treatment with either 3D or 2D as there was no worsening in HRQoL from baseline through to the end of the treatment period.

Secondly, Section 6.9 summarises the adverse events from the HCV clinical trial programme. In the SAPPHIRE trials, which evaluated safety outcomes for 3D + RBV vs placebo, there were no significant differences in the number of serious adverse events between 3D + RBV vs. placebo. Significant differences that were reported for some of the more common adverse events were mostly attributable to the co-administration of RBV. This is evidenced by the adverse event data from PEARL-II, PEARL-II and PEARL-IV which evaluated 3D alone with 3D + RBV, and there were significantly less adverse events for 3D vs. 3D + RBV.

Therefore, because AbbVie's regimens are interferon-free and all oral, they have the additional clinical benefit over existing treatments of a dramatically improved tolerability profile versus existing interferon containing regimens as well as removing the need to self-inject.

Strengths of the evidence base

There are a large number of strengths with regards to AbbVie's clinical evidence for HCV GT1 and HCV GT4. These strengths are summarised below:

- There is an extensive evidence base specifically in HCV GT1 compared to the comparators listed in the decision problem. AbbVie's 3D regimen has been studied in over 2,000 patients with HCV GT1 including sites in the UK. Furthermore, SVR rates are consistently high across a broad population of HCV patients that are reflective of those who will be eligible for treatment in the UK - namely treatment-naïve patients, treatment-experienced patients, those unsuitable for IFN based regimens, difficult-to-treat patients such as those with cirrhosis and in special populations such as those with HIV co-infection and those who have had a liver transplant.

- AbbVie is the first company to conduct a phase III trial solely in cirrhotic patients, a notoriously difficult-to-treat population. TURQUOISE-II was a large multinational study in 380 treatment naïve or treatment-experienced HCV GT1 patients with compensated cirrhosis. The overall SVR12 in treatment naïve and treatment-experienced patients receiving the licensed dose of 3D was 96.3%. This is considerably higher than any SVR results in cirrhotic patients reported for the comparator agents listed in the final scope. For treatment naïve cirrhotic patients the SVR rates for PegIFN/RBV, TPV + PegIFN/RBV, BOC + PegIFN/RBV, simeprevir + PegIFN/RBV and sofosbuvir + PegIFN/RBV were 33.3%, 61.9%, 31.3%, 60.4% and 80.8% respectively (see Table 58). The size of the TURQUOISE-II trial gives reassurance on the magnitude expected treatment effect in this difficult to treat patient population.

- In addition to the TURQUOISE-II cirrhotic trial, AbbVie conducted trials such as the SAPPHIRE or PEARL trials where specific patient populations of interest were the focus of the trials. For example, the PEARL trials focused on specific sub-genotypes in HVC GT1 and examined the safety and efficacy of AbbVie's 3D regimen with or without co-administered ribavirin. Importantly in PEARL-II and PEARL-III, administration of 3D alone resulted in both HCV GT1b-infected treatment naïve and treatment-experienced patients achieving 100% SVR12. SAPPHIRE-I focused specifically on treatment naïve HCV GT1 patients, whereas SAPPHIRE-II focused on treatment-experienced patients. Furthermore, all of AbbVie's treatment-experienced trials capped recruitment of partial responders and relapsers to previous PegIFN/RBV treatment to ensure that a large proportion of the more-difficult to treat previous null-responder patient population were included.

- The safety and efficacy of 3D has also been studied in special populations: HCV infected patients with HIV co-infection; post-transplant patients; and those receiving opioid replacement therapy. Whilst the trials in HIV co-infection and post-transplant have not yet completed, interim results from TURQUOISE-I (HIV co-infection) and CORAL-I (post-transplant) demonstrate that SVR12 rates are consistent with SVR12 rates reported in the phase 3 trials of HCV mono-infected subjects. In TURQUOISE-I, 100% subjects with genotype 1b infection and 91.1% subjects with genotype 1a infection achieved SVR12. In CORAL-I, 100% subjects with genotype 1b infection and 96.6% subjects with genotype 1a infection achieved SVR12. In the opioid replacement study 97.4% patients achieved SVR12. These data show that consistently high SVR rates are achievable with 3D.

- In comparison to other directly acting anti-viral agents, AbbVie conducted a relatively large study in both treatment naïve and treatment experienced HCV GT4 infected subjects (n=135). Furthermore, as mentioned in Section 6.10.1, 100% SVR rates were achieved for both treatment naïve and treatment experienced patients receiving 2D + RBV. Therefore, this sample size provides a greater degree of certainty that patients with HCV GT4 in the UK will achieve SVR if they receive 2D + RBV compared to other agents.

Economic evaluation

Type of economic evaluation and justification for the approach used:

To estimate the impact of achieving SVR (virologic cure) on final outcomes for patients infected with either GT1 or GT4 chronic hepatitis C, an appropriate model of the natural history was required, taking into account different disease states associated with HCV disease progression. AbbVie's economic evaluation used a model structure developed by the University of Southampton which has been considered appropriate for decision making in a number of prior NICE appraisals.

The model simulates the lifetime disease progression of persons with chronic HCV infection and is aligned with the clinical pathway of care described in section 2.5 of the submission. Thus, consistent with Shepherd et al., 2007 and Hartwell et al., 2011 the three initial fibrosis stages are characterised by mild fibrosis (Metavir score F0-F1), moderate fibrosis (F2-F3), and compensated cirrhosis (F4), with possible transitions occurring annually. All treatment and treatment-related outcomes occur within the first model year, which coincides with the first cycle in the model structure. Following treatment, patients who do not achieve SVR are at risk of progressive liver disease, and are assumed to face the same risks of disease progression as untreated patients. In the absence of successful treatment, patients may remain in their existing health state or may progress to more severe stages of liver disease. A proportion of patients with compensated cirrhosis progress to DCC and HCC.

The same model structure is used for treatment-naïve and treatment-experienced patients with genotype 1 and genotype 4.

Cost-effectiveness results:

The mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation's base-case are summarised in Table 2 through to Table 5 below:

Table 2: Base-case cost-effectiveness results for GT1, Treatment- naïve, IFN-eligible patients

Intervention (3D) versus comparators in GT1, Tx naïve, IFN-eligible patients	**Regimen Cost**			**Medical/Other Cost (Discounted)**		**Total Cost**	**QALYs**	**ICER**
	PR	DAA	Total	Treatment-related AE	Medical			
3D	£692	£37,078	£37,771	£41	£5,813	**£43,624**	**15.21**	**Dominant**
SOF+PR	£2,528	£34,606	£37,133	£360	£6,844	**£44,337**	**15.01**	
Incremental (Intervention -Comparator 1)	-£1,835	£2,472	£637	-£318	-£1,032	**-£713**	**0.21**	
TPR+PR	£6,032	£19,467	£25,499	£425	£9,963	**£35,887**	**14.55**	**£11,677**
Incremental (Intervention -Comparator 2)	-£5,340	£17,611	£12,271	-£383	-£4,150	**£7,738**	**0.66**	
PR	£7,970	£0	£7,970	£362	£14,540	**£22,872**	**13.72**	**£13,864**
Incremental (Intervention -Comparator 3)	-£7,277	£37,078	£29,801	-£321	-£8,728	**£20,752**	**1.50**	
BOC+PR	£5,843	£13,896	£19,739	£672	£11,736	**£32,147**	**14.22**	**£11,572**
Incremental (Intervention -Comparator 4)	-£5,150	£23,182	£18,032	-£631	-£5,923	**£11,478**	**0.99**	

Table 3: Base-case cost-effectiveness results for GT1, treatment-experienced, IFN-eligible patients

Intervention (3D) versus comparators in GT1, Tx experienced, IFN-eligible patients	Regimen Cost			Medical/Other Cost (Discounted)			Total Cost	QALYs	ICER
	P±R	DAA	Total	Treatment-related AE	Medical				
3D	£881	£42,131	£43,012	£53	£8,816		**£51,882**	**13.19**	#VALUE!*
SOF+PR	#VALUE!	#VALUE!	#VALUE!	£0	#VALUE!		#VALUE!	#VALUE!	
Incremental (Intervention -Comparator 1)	#VALUE!	#VALUE!	#VALUE!	£53	#VALUE!		#VALUE!	#VALUE!	
TPR+PR	£8,299	£18,188	£26,487	£397	£15,762		**£42,646**	**12.10**	**£8,507**
Incremental (Intervention -Comparator 2)	-£7,418	£23,943	£16,525	-£344	-£6,945		**£9,236**	**1.09**	
PR	£7,046	£0	£7,046	£322	£22,760		**£30,128**	**11.07**	**£10,258**
Incremental (Intervention -Comparator 3)	-£6,165	£42,131	£35,967	-£268	-£13,944		**£21,754**	**2.12**	
BOC+PR	#VALUE!	#VALUE!	#VALUE!	£0	#VALUE!		#VALUE!	#VALUE!	#VALUE!
Incremental (Intervention -Comparator 4)	#VALUE!	#VALUE!	#VALUE!	£53	#VALUE!		#VALUE!	#VALUE!	

*#VALUE indicates no possible comparison

Table 4: Base-case cost-effectiveness results for GT4, Treatment naïve, IFN-eligible patients (non-cirrhotic only)

Intervention (2D) versus comparators in GT4, Tx naive, IFN-eligible patients	Regimen Cost			Medical/Other Cost (Discounted)			Total Cost	QALYs	ICER
	PR	DAA	Total	Treatment-related AE	Medical				
2D	£878	£31,817	£32,695	£51	£3,744		**£36,490**	**15.84**	**Dominant**
SOF+PR	£2,528	£34,606	£37,133	£360	£3,744		**£41,237**	**15.81**	
Incremental (Intervention -Comparator 1)	-£1,650	-£2,788	-£4,438	-£309	£0		**-£4,747**	**0.04**	
PR	£10,127	£0	£10,127	£362	£8,797		**£19,286**	**15.00**	**£20,351**
Incremental (Intervention -Comparator 2)	-£9,248	£31,817	£22,569	-£311	-£5,053		**£17,204**	**0.85**	

Table 5: Base-case cost-effectiveness results for GT4, Treatment experienced, IFN-eligible patients (non-cirrhotic only)

Intervention (2D) versus comparators in GT4, Tx experienced, IFN-eligible patients	Regimen Cost (Discounted)			Medical/Other Cost (Discounted)			Total Cost	QALYs	ICER
	PR	DAA	Total	Treatment-related AE	Medical	Indirect			
2D	£889	£32,201	£33,089	£51	£3,396	£0	**£36,536**	**14.84**	**£8,977**
No treatment	£0	£0	£0	£0	£16,186	£0	**£16,186**	**12.58**	
Incremental (Intervention -Comparator 1)	£889	£32,201	£33,089	£51	-£12,790	£0	**£20,350**	**2.27**	

Incremental cost-effectiveness results:

HCV GT1:

Table 6: Base-case results for GT1, treatment-naïve, interferon eligible patients

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£22,872	19.68	13.72	NA	NA	NA	NA	NA
Boceprevir + PR	£32,147	19.94	14.22	£9,275	0.26	0.50	£18,366	Extended dominance
Telaprevir + PR	£35,887	20.16	14.55	£13,014	0.48	0.83	£15,602	Extended dominance
AbbVie Regimen	£43,624	20.59	15.21	£20,752	0.91	1.50	£13,864	£13,864
Sofosbuvir + PR	£44,337	20.46	15.01	£21,465	0.78	1.29	£16,618	Dominated

Table 7: Base-case results for GT1, treatment-experienced (overall) interferon eligible patients

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£30,128	17.13	11.07	NA	NA	NA	NA	NA
Telaprevir + PR	£42,646	17.92	12.10	£12,518	0.78	1.04	£12,095	Extended dominance
AbbVie Regimen	£51,882	18.72	13.19	£21,754	1.58	2.12	£10,258	£10,258

HCV GT4:

Table 8: GT4, treatment-naïve, interferon-eligible patients (non-cirrhotic only)

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental

PR	£19,286	20.58	15.00	NA	NA	NA	NA	NA
AbbVie Regimen	£36,490	20.98	15.84	£17,204	0.40	0.85	£20,351	£20,351
Sofosbuvir + PR	£41,237	20.98	15.81	£21,951	0.40	0.81	£27,135	Dominated

Table 9: GT4, treatment-experienced (overall) interferon eligible patients (non-cirrhotic only)

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. NT	ICER incremental
No treatment (NT)	£16,186	18.57	12.58	NA	NA	NA	NA	NA
AbbVie Regimen	£36,536	19.71	14.84	£20,350	1.14	2.27	£8,977	£8,977

Subgroup analyses considered and cost-effectiveness results:

Table 10: Incremental analysis for GT1a, treatment-naïve (IFN-eligible) patients

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£23,305	19.63	13.64	NA	NA	NA	NA	NA
Boceprevir + PR	£32,905	19.86	14.09	£9,601	0.22	0.45	£21,411	Extended dominance
Telaprevir + PR	£36,378	20.10	14.47	£13,073	0.47	0.82	£15,865	Extended dominance
Sofosbuvir + PR	£44,064	20.49	15.06	£20,760	0.85	1.41	£14,680	Extended dominance
AbbVie Regimen	£45,110	20.57	15.18	£21,805	0.93	1.54	£14,199	£14,199

Table 11: Incremental analysis for GT1b, treatment-naïve (IFN-eligible) patients

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental	Incremental	Incremental	ICER vs. PR	ICER

				costs, £	LYGs	QALYs		incremental
PR	£22,190	19.76	13.84	NA	NA	NA	NA	NA
Boceprevir + PR	£31,832	19.98	14.28	£9,642	0.22	0.44	£21,855	Extended dominance
Telaprevir + PR	£35,210	20.23	14.67	£13,020	0.48	0.83	£15,627	Extended dominance
AbbVie Regimen	£40,348	20.64	15.29	£18,159	0.88	1.46	£12,453	£12,453
Sofosbuvir + PR	£45,516	20.33	14.80	£23,327	0.57	0.97	£24,084	Dominated

Table 12: GT1a, treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£29,458	17.22	11.16	NA	NA	NA	NA	NA
Telaprevir + PR	£43,559	17.81	11.96	£14,101	0.59	0.80	£17,543	Extended dominance
AbbVie Regimen	£55,552	18.71	13.17	£26,093	1.50	2.01	£12,978	£12,978

Table 13: GT1b, treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£30,738	17.06	10.98	NA	NA	NA	NA	NA
Telaprevir + PR	£41,579	18.04	12.26	£10,841	0.98	1.28	£8,474	Extended dominance
AbbVie Regimen	£43,790	18.72	13.22	£13,052	1.66	2.24	£5,828	£5,828
PR								

Table 14: GT1, treatment-experienced (null responders) interferon eligible

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental

PR	£31,630	16.98	10.82	NA	NA	NA	NA	NA
Telaprevir + PR	£47,701	17.34	11.29	£16,072	0.36	0.47	£34,310	Extended dominance
AbbVie Regimen	£52,089	18.69	13.16	£20,459	1.70	2.34	£8,755	£8,755

Table 15: GT1, treatment-experienced (partial responders) interferon eligible

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£29,486	17.23	11.11	NA	NA	NA	NA	NA
Telaprevir + PR	£43,041	17.80	12.10	£13,555	0.57	1.00	£13,622	Extended dominance
Boceprevir + PR	£47,403	17.32	11.48	£17,917	0.09	0.38	£47,644	Extended dominance
AbbVie Regimen	£51,770	18.72	13.21	£22,284	1.48	2.11	£10,584	£10,584

Table 16: treatment-experienced (prior relapsers) interferon eligible

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£29,483	17.17	11.22	NA	NA	NA	NA	NA
Telaprevir + PR	£38,558	18.43	12.71	£9,075	1.26	1.49	£6,091	£6,091
Boceprevir + PR	£42,763	17.86	12.18	£13,280	0.69	0.96	£13,875	Dominated
AbbVie Regimen	£51,811	18.74	13.19	£22,328	1.56	1.97	£11,334	£27,601

Table 17: GT1, treatment-naïve interferon unsuitable

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. NT	ICER incremental
No treatment	£19,788	19.01	12.70	NA	NA	NA	NA	NA

AbbVie Regimen	£43,624	20.59	15.21	£23,837	1.58	2.51	£9,498	£9,498

Table 18: GT1, treatment-experienced (overall) interferon unsuitable

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. NT	ICER incremental
No treatment	£24,245	16.84	10.80	NA	NA	NA	NA	NA
AbbVie Regimen	£51,882	18.72	13.19	£27,637	1.88	2.38	£11,597	£11,597

Table 19: GT4, treatment-naïve interferon unsuitable (non-cirrhotics only)

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. NT	ICER incremental
No treatment	£17,230	19.62	13.31	NA	NA	NA	NA	NA
AbbVie Regimen	£36,490	20.98	15.84	£19,260	1.36	2.53	£7,614	£7,614

In conclusion, the 3D regimen for genotype 1 patients and the 2D regimen for genotype 4 patients is a step change in the management of hepatitis C compared to current standard of care. These interferon-free regimens have the benefits of being all oral therapies with a dramatically improved tolerability and efficacy profile versus existing interferon containing regimens. These regimens should be considered highly cost effective therapies for reducing the public health burden of HCV infection in England and Wales.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

There are two regimens included in this submission, the first for the treatment of chronic hepatitis C genotype 1 (HCV GT1) and the second for the treatment of chronic hepatitis C genotype 4 (HCV GT4):

HCV GT1
G*eneric name*: ombitasvir/paritaprevir/ritonavir with dasabuvir (3D)

Alternative names: ABT-267/ ABT-450/r/ and ABT-333

Brand name: Viekirax and Exviera

For simplicity, AbbVie has referred to this regimen as 3D within this document, as there are three directly acting anti-viral agents in the intervention. Ritonavir is included in the formulation as a pharmacokinetic enhancer for paritaprevir. The inclusion of ritonavir in the 3D regimen reduces the metabolism of paritaprevir, allowing for a once-daily dosing of paritaprevir and overall lower dose requirement. The amount of ritonavir equates to a total daily dose of just 100mg.

Therapeutic class: the three directly acting anti-viral agents belong to the following classes:

Ombitasvir: HCV NS5A inhibitor
Paritaprevir: non-structural protein [NS] 3/4A protease inhibitor
Dasabuvir: non-nucleoside HCV NS5B RNA polymerase inhibitor

HCV GT4
Generic name: ombitasvir/paritaprevir/ritonavir (2D)

Alternative names: ABT-267/ABT-450/r

Brand name: Viekirax

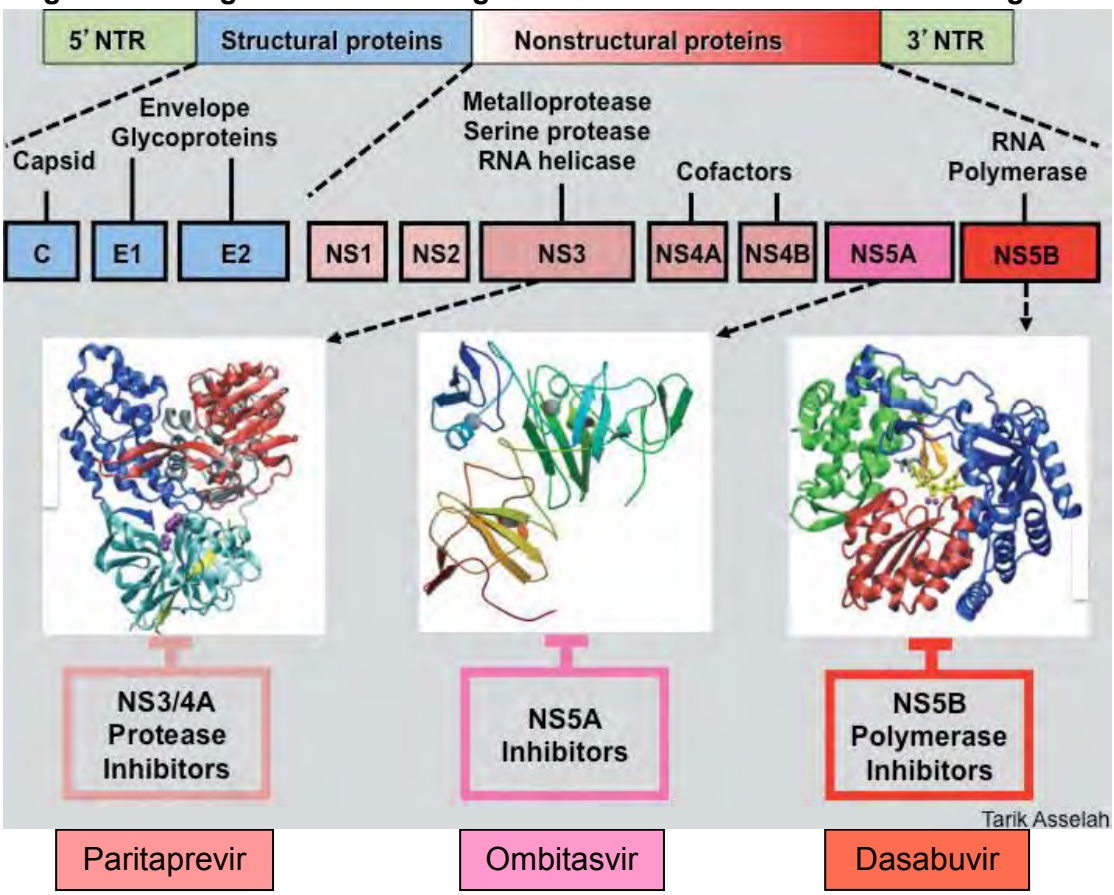
Again, for simplicity, AbbVie has referred to this regimen as 2D within this document, as there are two directly acting anti-viral agents in the intervention. Ritonavir is included in the formulation as a pharmacokinetic enhancer for paritaprevir. As above, the inclusion of ritonavir in the 3D regimen reduces the metabolism of paritaprevir, allowing for a once-daily dosing of paritaprevir and overall lower dose requirement. The amount of ritonavir equates to a total daily dose of just 100mg.

Therapeutic class:
Ombitasvir: HCV NS5A inhibitor
Paritaprevir: non-structural protein [NS] 3/4A protease inhibitor

1.2 What is the principal mechanism of action of the technology?

The HCV life cycle begins with virion attachment to its specific receptor. The HCV RNA genome serves as a template for viral replication and as a viral messenger RNA for viral production. It is translated into a polyprotein that is cleaved by proteases. Then, viral assembly occurs. AbbVie's HCV regimens inhibit HCV viral replication by targeting multiple stages of the HCV life cycle. Figure 1 illustrates the HCV genome and which enzymes AbbVie's regimens specifically target.

Figure 2: HCV genome illustrating mechanism of action for AbbVie's regimens



The NS3 serine protease domain associates with the NS4A cofactor to cleave four specific sites. Paritaprevir inhibits this NS3 serine protease activity. The NS5A is a membrane-associated phosphoprotein present in basally phosphorylated (p56) and hyperphosphorylated (p58) forms. NS5A inhibitors, like ombitasvir block hyperphosphorylation of NS5A, which is believed to play an essential role in the viral life cycle. Polymerase inhibitors, like dasabuvir, interfere with viral replication by binding to the NS5B RNA-dependent RNA polymerase.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state

current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

At the time of writing this submission, AbbVie's 3D and 2D regimens do not have a UK marketing authorisation. AbbVie provided two full submissions to EMA via the Centralised procedure for new active substances in May 2014. CHMP positive opinion was granted on 21st November 2014. Subsequent regulatory approval expected January 2015 along with the anticipated UK marketing authorisation. Pending all necessary approvals, AbbVie intends to launch its HCV regimens from January 2015.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

In the draft assessment report from EMA there was some discussion as to which patients will also need concomitant ribavirin with either 3D or 2D. It was decided that treatment naïve and treatment-experienced HCV GT1b infected patients would not require concomitant ribavirin. HCV GT1a, GT4 and cirrhotics would have co-administered ribavirin with either 3D or 2D.

In addition, there was some discussion around the expected dosing regimen of 3D in GT1a treatment experienced HCV patients with cirrhosis. It was decided that these patients would receive 24 weeks of 3D + RBV, but some patients may receive 12 weeks treatment dependent on clinician experience and certain prognostic factors.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Ombitasvir/paritaprevir/ritonavir is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults. Dasabuvir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C. Table 20 below details the treatment regimen and duration by patient population as outlined in the draft SPC submitted to EMA.[1]

Table 20: Treatment regimen and duration by patient population

Patient population	Treatment	Duration
Genotype 1b without cirrhosis	3D	12 weeks
Genotype 1b with cirrhosis	3D + ribavirin	
Genotype 1a without cirrhosis	3D + ribavirin*	
Genotype 1a with cirrhosis	3D + ribavirin*	24 weeks (see section 5.1 of SPC)

Genotype 4, without cirrhosis	2D + ribavirin	12 weeks
Genotype 4, with cirrhosis	2D + ribavirin	24 weeks

* Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There are a large number of completed and ongoing studies investigating AbbVie's regimens for the treatment of chronic HCV infection - https://clinicaltrials.gov/ct2/results?term=abt450&Search=Search. Of these, 12 phase II and III trials have completed. Seventeen studies are currently ongoing, however a number of them won't complete within the next 12 months. The following trials are likely to provide results within the timeframe, the details of which are provided below:

- **MALACHITE-I (M13-774) and MALACHITE-II (M13-862) – HCV GT1 head to head trials vs. telaprevir**

The aim of these head-to-head randomised, open-label studies is to evaluate the efficacy and safety of AbbVie's 3D regimen co-administered with RBV vs. telaprevir + PegIFN + RBV in both treatment naïve (MALACHITE I) and treatment experienced (MALACHITE II) patients with HCV GT1. The primary efficacy endpoint is the percentage of patients with SVR 12 weeks post-treatment. Final data collection for the primary outcome measure is expected December 2014 for MALACHITE I and MALACHITE II.

- **TURQUOISE-I (M14-004) – HIV co-infection**

The aim of this randomised, open-label study is to evaluate the safety and efficacy AbbVie's 3D regimen co-administered with RBV for the treatment of HCV GT1 and HIV co-infection. The primary efficacy endpoint is the percentage of patients with SVR 12 weeks post-treatment. Final data collection for the primary outcome measure is expected September 2015; preliminary data were presented at AASLD in November 2014 and are included in this submission.

- **CORAL-I (M12-999) – Post-transplant study**

This open-label phase II trial is evaluating the safety and efficacy of AbbVie's 3D regimen with or without co-administered RBV in adult liver transplant recipients with HCV GT1 infection. The primary efficacy endpoint is the percentage of patients with SVR 12 weeks post-treatment. Final data collection for the primary outcome measure is expected December 2015. However, preliminary data are available and are included in this submission.

- **TURQUOISE-CPB (M14-227) – HCV GT1 with decompensated cirrhosis**

A randomised, open-label, study to evaluate the safety and efficacy of AbbVie's 3D regimen co-administered with RBV in adults with genotype 1 HCV infection and

decompensated cirrhosis. Final data collection for the primary outcome measure is expected July 2015.

- **TURQUOISE-III (M14-490) – HCV GT1b with cirrhosis (without RBV)**

An open-label, single-arm study to evaluate the safety and efficacy of AbbVie's 3D regimen in adults with genotype 1b HCV infection and cirrhosis. Final data collection for the primary outcome measure is expected May 2015.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is anticipated that the AbbVie regimens will be launched in January 2015.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

No. AbbVie's regimens are currently undergoing FDA and EMA assessment. FDA approval is expected December 2014 and following CHMP positive opinion in November 2014, EMA approval is expected in January 2015.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

AbbVie intends to submit to the SMC in January 2015, which would result in guidance published on the SMC website in May 2015.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 21: Costs of technology being appraised

Pharmaceutical formulation	Film coated tablets
Acquisition cost (excluding VAT)	The acquisition cost of 3D is £11,666.66 for 28 day's supply. The acquisition cost of 2D is £10,733.33 for 28 day's supply.
Method of administration	Oral
Doses	The recommended dose of AbbVie's oral regimens: **HCV GT1**: 12.5 mg ombitasvir/ 75 mg paritaprevir/ 50 mg ritonavir and 250mg dasabuvir **HCV GT4**: 12.5 mg ombitasvir/ 75 mg paritaprevir/ 50 mg ritonavir
Dosing frequency	**HCV GT1:** Two 12.5 mg ombitasvir/ 75 mg paritaprevir/ 50 mg ritonavir tablets once daily (in the morning) taken with one 250mg dasabuvir twice daily (morning and evening). The tablets should be taken with food. **HCV GT4:** Two 12.5 mg ombitasvir/ 75 mg paritaprevir/ 50 mg ritonavir tablets once daily with food.
Average length of a course of treatment	12 weeks 24 weeks of 3D + ribavirin is recommended for patients with compensated cirrhosis who are infected with HCV genotype 1a or genotype 4.
Average cost of a course of treatment	The average cost of a 12 week course of treatment of 3D is £34,999.98 The average cost of a 24 week course of treatment of 3D is £69,999.96. The average cost of a 12 week course of treatment of 2D is £32,199.99 The average cost of a 24 week course of treatment of 3D is £64,399.98
Anticipated average interval between courses of treatments	Not applicable.
Anticipated number of repeat courses of treatments	Not applicable.
Dose adjustments	Dose adjustments are not recommended.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide

details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Not applicable. Patients will already be characterised by genotype, including sub-genotype, upon diagnosis or before commencing treatment, and there are no additional tests required to administer either 3D or 2D.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No. Based on advice sought from clinical experts, AbbVie anticipates that there is likely to be less monitoring required with AbbVie's regimens compared with usual clinical practice e.g. for PegIFN containing regimens. Patients treated with current standards of care are managed using a response guided therapy approach, where virologic response measured at specific on-treatment time points is used to determine the likelihood of SVR and the required treatment duration. Treatment duration then ranges from 24 to 48 weeks dependent on the outcome of these measures. The side effects associated with PegIFN + RBV based therapies also necessitate regular monitoring of these patients and there are important stopping rules for both futility and safety required with both telaprevir and boceprevir based-therapy.

In contrast, 3D and 2D are 12 week treatment regimens with the exception of patients with compensated cirrhosis infected with HCV GT1a or GT4, who require 24 weeks treatment. As AbbVie's regimens are PegIFN free, there is no need to check for rapid virologic response at week 4 to determine whether the patient is likely to respond to PegIFN, and the potential for side effects is considerably reduced, significantly reducing the amount of monitoring required.

Therefore treatment with AbbVie's regimens should simplify patient management considerably relative to current standards of care and also reduce the need for frequent on-treatment viral load monitoring and clinic visits, which often require patients to travel to specialist treatment centres.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

AbbVie's regimens are interferon-free, however some patients require co-administration with ribavirin. Table 20 summarises the patient populations for 3D and 2D that require co-administered ribavirin as part of a course of treatment. In summary, patients with HCV genotype 1b without cirrhosis do not require co-

administered ribavirin, but it is recommended that all other GT1 and GT4 patients, with and without cirrhosis, receive either 3D or 2D + ribavirin. However, 3D without ribavirin can be considered as a therapeutic option for treatment-naïve HCV patients with genotype 1a infection without cirrhosis who are intolerant or ineligible for ribavirin. Treatment decision should be guided by an assessment of the potential benefits and risks for the individual patient. The removal of ribavirin from the treatment regimen further reduces the potential for side effects and reduces the overall cost.

2 Context

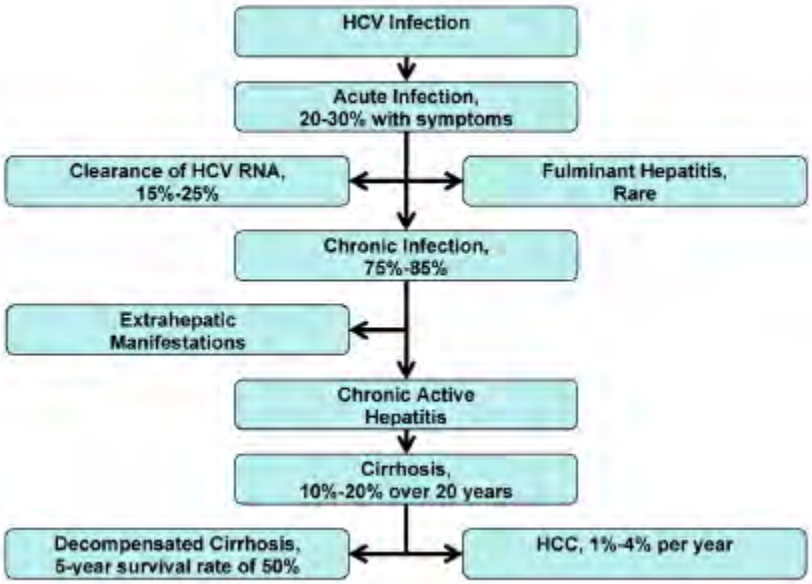
2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Chronic hepatitis C infection is associated with significant morbidity, mortality and economic burden. It is the most common cause of chronic liver disease and cirrhosis, and is the most common indication for liver transplantation in the US and most of Europe.[2,3] Hepatitis C is a progressive disease caused by the hepatitis C virus (HCV) which infects the liver. The virus itself is an RNA virus that belongs to the family flaviviridae. HCV replicates in the cytoplasm of hepatocytes, but is not directly cytopathic. Persistent infection appears to rely on rapid production of virus and continuous cell-to-cell spread, along with a lack of vigorous T-cell immune response to HCV antigens. The HCV turnover rate can be quite high with replication ranging between 1010 to 1012 virions per day, and a predicted viral half-life of 2 to 3 hours. The rapid viral replication and lack of error proofreading by the viral RNA polymerase are reasons why the HCV RNA genome mutates frequently. There are six known genotypes (numbered 1 through 6) and more than 50 subtypes (e.g.,1a, 1b, 2a...).[4]

Acute infection is generally asymptomatic and between 15-25% of acutely affected individuals will gradually show a decrease in virus levels and clear the virus; however the remaining 75-85% will go on to develop chronic HCV infection defined as persistent, detectable serum HCV RNA for a period greater than 6 months (Figure 3). Between 5% and 25% of individuals with chronic HCV go on to develop cirrhosis over a 20-30 year period and are at risk of progression to decompensated cirrhosis and hepatocellular carcinoma (HCC) and therefore at risk of dying from liver related complications (Figure 3).[4] Compared with non-infected patients, the risk of developing HCC is 17- fold higher in HCV infected patients,[4] with patients diagnosed with HCC having a 33% probability of death during the first year.[5]

The rate at which liver disease progresses is unpredictable and related to a range of environmental and host factors, including alcohol consumption, age at infection, gender, the presence of co-morbidities such as obesity or insulin resistance, and co-infection with hepatitis B virus infection or HIV.[3,4] In the setting of persistent hepatitis C, the rate of progression of liver fibrosis varies widely. There have been a number of studies focusing on the natural course of disease progression from chronic hepatitis C to cirrhosis, HCC, and death. Liver biopsy is still the gold standard for the grading and staging of chronic hepatitis C, however Fibroscans are also now used in routine clinical practice, as they are less intrusive. The activity of liver disease or grade, is gauged by the number of mononuclear inflammatory cells present in and around the portal areas, and by the number of dead or dying hepatocytes. The structural liver damage, also known as fibrosis, is variable in chronic HCV infection. Fibrosis implies possible progression to cirrhosis. In mild cases, fibrosis is limited to the portal and periportal areas. More advanced changes are defined by fibrosis that extends from one portal area to another, also known as "bridging fibrosis." Progression to cirrhosis is often clinically silent, apart from nonspecific symptoms such as fatigue, upper right quadrant pain or, sometimes, arthralgia and myalgia. Some patients are not known to have chronic HCV until they present with the complications of end-stage liver disease or HCC.[4]

Figure 3: Natural history of HCV infection



Source: Chen and Morgan, 2006.[4]

HCV has also been found to replicate in sites outside the liver, including bone marrow, the central nervous system, endocrine glands, lymphatic tissue and skin cells. This can result in a host of extra-hepatic manifestations, including autoimmune disease, skin reactions, renal injury and neuropathy; it is estimated that up to 76% of patients with chronic HCV experience at least one such manifestation.[4] These extra-hepatic manifestations contribute considerably to the overall disease burden in chronic HCV patients.[6]

Chronic HCV also leads to impairment in quality of life (QoL) with patients feeling unwell in terms of both their physical and mental well-being.[7,8] In addition to a reduced quality of life, patients also have to manage with the social stigma associated with chronic HCV, particularly around its connotations with intravenous drug use.[9]

The most recent national estimates suggest that around 214,000 individuals are chronically infected with HCV in the UK.[10] Genotype 1 (GT1) is the most prevalent HCV genotype in the UK accounting for 45% of cases. [10] Genotypes 2 and 3 account for approximately 40-50% of cases and the last 5% of infections is comprised of GT4, 5 and 6.[11]

While the incidence of HCV infection isn't increasing and may actually be declining, the prevalence of hepatitis C related cirrhosis and its complications are set to continue to rise as those patients infected in the 1980s and 1990s begin to develop complications. Health Protection England has estimated that in 2000 there were 4,310 people with HCV related cirrhosis and by 2010 this number had more than doubled to 9,670.[11] It is estimated that if left untreated by 2020 15,840 individuals in England alone will be living with hepatitis C-related cirrhosis or liver cancer, with more than 4,200 with decompensated cirrhosis or liver cancer for whom a liver transplant may be the only option.[11]

The primary goal of HCV treatment is eradication of the virus from the blood in order to prevent progression of liver disease and the complications of HCV-related liver

disease including fibrosis, cirrhosis, HCC, death and secondarily to prevent the transmission of HCV.[12] Successful treatment (referred to as a cure) is indicated by a sustained virological response (SVR) defined as an undetectable serum HCV RNA 12 weeks after treatment has been stopped. SVR is considered to indicate a permanent resolution of infection and be synonymous with a cure although relapse may occur in approximately 5% of people after 5 years.[13] Achievement of SVR leads to a regression of fibrosis and cirrhosis and has been associated with a reduced rate of hepatic decompensation, a reduced risk for HCC and both a reduced rate of liver and non-liver related mortality.[14,15,16]

Prior to 2011, standard of care consisted of treatment with PegIFN and RBV (dual therapy). In 2011, the first directly acting antivirals (DAAs) for the treatment of HCV GT1 infection were introduced. These were the protease inhibitors (PIs) telaprevir and boceprevir, and both are used in combination with PegIFN and RBV (triple therapy) for patients with HCV GT1. These NICE approved regimens considerably improved outcomes for HCV GT1 patients, but are not indicated for any other genotype. PegIFN in combination with RBV remains the standard of care for GT4 patients.

In 2014, sofosbuvir + PegIFN + RBV, and simeprevir + PegIFN + RBV received marketing authorisations for the treatment of chronic hepatitis C and offer the potential for higher SVR rates then telaprevir and boceprevir based therapy for GT1 patients and dual therapy for GT4. However, all these regimens contain PegIFN, which is associated with long and complicated treatment regimens and frequently intolerable side-effects, which can lead to treatment failure. Furthermore, for those patients who are interferon-unsuitable (including those in whom interferon is contraindicated, who are interferon intolerant or who are unwilling to take interferon) there are limited treatment options available. Because not all treatment options are licensed for all genotypes there is the potential for inequity of access related to a given treatment and the potential opportunity to achieve virologic cure amongst the infected population.

Given the well-documented and harmful side effects of interferon, its elimination from the treatment regimen would represent a significant advance and step-change from the current interferon-based regimens. Interferon-based regimens have demonstrated poor tolerability and adherence, limiting their uptake and reducing the likelihood of achieving SVR. The 2014 Public Health England report indicates that only 3% of patients with long-term infection are starting treatment each year.[10] Furthermore, of the HCV GT1 patients taking PegIFN + RBV, sentinel surveillance data suggest that rates of SVR (estimated for people identified as undergoing a first course of treatment between 2009 and 2012), were 54% in those with genotype 1 and 69% in those with non-1 genotypes; and equivalent SVR rates for 2012 alone remained unchanged at 54% for GT1. [10]

AbbVie's all-oral, interferon-free anti-viral combination thus has the potential to significantly improve patients' HRQoL by allowing greater numbers of patients, including those who are not eligible for or intolerant to the current regimens, to receive shorter, more efficacious and more tolerable therapy.

With the increasing burden of chronic HCV the effective treatment of patients is essential in order to avoid progression of the disease and the associated complications, including excess mortality.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

The number of patients in England and Wales for which the technology is indicated are summarised in Table 22 below.

Table 22: Number of patients with HCV eligible for AbbVie's regimens in England and Wales

Total number of adults in England and Wales	42,170,704
Prevalence of HCV in adult population – 0.4-0.75%	214,000
People that are HCV RNA positive – 66%	141,240
People with GT1 - 45%	63,558
People with GT4 - 2%	2,824
Total number of people eligible for treatment	66,382
Percentage of HCV patients treated in 2013 – 3%	1,991

Source: Public Health England: Hepatitis C – updated report 31 July 2014.[10]

According to the Public Health England report, only 3% of patients with chronic HCV were treated in England last year. Given that AbbVie's oral Peg-IFN free regimens will allow patients to receive a shorter, more efficacious and more tolerable therapy, it is likely that this number will increase. It is worth noting that the opportunity to treat more patients is anticipated to have a significant positive impact on the incidence of HCV-related end-stage liver disease / HCC. Preliminary results from statistical models suggest if the numbers of patients treated are doubled over the next 10 years an estimated total of 5,880 additional cases of HCV-related end – stage liver disease / HCC could be averted over the next 30 years.[11]

Further details on patient numbers have been provided in Section 8.1 of this document.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

While there are data clearly demonstrating that chronic HCV is associated with increased morbidity and mortality, published data on the actual life expectancy of people with chronic HCV is limited and dependent on the degree of liver fibrosis and ongoing behaviour, especially alcohol consumption.

A cohort study conducted in England compared the death rates of 2,286 patients with HCV infection to that seen in an age and sex-matched English population and found that standardised mortality rates were three times higher than those expected in the general population.[17] Section 7 explains how mortality has been incorporated into the economic model using data from Shepherd *et al.*

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

The following NICE technology appraisal guidance is available.

Guidance number / Issue date	Title	Guidance recommendations
TA253 / April 2012	Boceprevir for the treatment of genotype 1 chronic hepatitis C	1.1 Boceprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease: • who are previously untreated or • in whom previous treatment has failed.
TA252 / April 2012	Telaprevir for the treatment of genotype 1 chronic hepatitis C	1.1 Telaprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease: • who are previously untreated or • in whom previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin has failed, including people whose condition has relapsed, has partially responded or did not respond**.**
TA200 / September 2010	Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C	1.1 Combination therapy with peginterferon alfa (2a or 2b) and ribavirin is recommended as a treatment option for adults with chronic hepatitis C: • who have been treated previously with peginterferon alfa (2a or 2b) and ribavirin in combination, or with peginterferon alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed **or** • who are co-infected with HIV. 1.2 Shortened courses of combination therapy with peginterferon alfa (2a or 2b) and ribavirin are recommended for the treatment of adults with chronic hepatitis C who: • have a rapid virological response to treatment at week 4 that is identified by a highly sensitive test and • are considered suitable for a shortened course of treatment. 1.3 When deciding on the duration of combination therapy, clinicians should take into account the licensed indication of the chosen drug (peginterferon alfa-2a or peginterferon alfa-2b), the genotype of the hepatitis C virus, the viral load at the start of treatment and the response to treatment (as indicated by the viral load).
TA106 / August 200631	Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C.	1.1 Combination therapy, comprising peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin, is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C.

	This is an extension of the guidance given in NICE technology appraisal guidance 75	1.2 Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C for people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated. 1.3 The decision on whether a person with mild chronic hepatitis C should be treated immediately or should wait until the disease has reached a moderate stage ('watchful waiting') should be made by the person after fully informed consultation with the responsible clinician. The decision to treat need not depend on a liver biopsy to determine the stage of the disease if treatment is initiated immediately. However, a biopsy may be recommended by the clinician for other reasons or if a strategy of watchful waiting is chosen. 1.4 There is insufficient evidence to recommend combination therapy or monotherapy with peginterferon alfa for people with mild chronic hepatitis C who are under the age of 18 years, or those who have had a liver transplant.
TA75 / January 200425	Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C This guidance is a review and extension of Technology Appraisal Guidance No. 14 issued in October 2000	1.1 Combination therapy with peginterferon alfa and ribavirin is recommended within its licensed indications for the treatment of people aged 18 years and over with moderate to severe chronic hepatitis C (CHC), defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation. 1.2 People with moderate to severe CHC are suitable for treatment if they have: • not previously been treated with interferon alfa or peginterferon alfa, or • been treated previously with interferon alfa (as monotherapy or in combination therapy), and/or 1.3 People currently being treated with interferon alfa, either as combination therapy or monotherapy, may be switched to the corresponding therapy with peginterferon alfa. 1.4 Treatment for the groups identified in Sections 1.1 and 1.2 should be as follows. • People infected with hepatitis C virus (HCV) of genotype 2 and/or 3 should be treated for 24 weeks. • For people infected with HCV of genotype 1, 4, 5 or 6, initial treatment should be for 12 weeks. Only people showing, at 12 weeks, a reduction in viral load to less than 1% of its level at the start of treatment (at least a 2-log reduction, see Section 4.1.2.5) should continue treatment until 48 weeks. For people in whom viral load at 12 weeks exceeds 1% of its level at the start of treatment, treatment should be discontinued. • People infected with more than one genotype that includes one or more of genotypes 1, 4, 5, or 6 should be treated as for genotype 1. (Recommendation 1.4 still applies for people who are treated with standard courses of combination therapy, but has been replaced by NICE technology appraisal guidance 200 [TA200] for people who are eligible for shortened courses of combination therapy [as described in recommendation 1.2 of TA200]) 1.5 People satisfying the conditions in Sections 1.1 and 1.2 but for whom ribavirin is contraindicated or is not tolerated should be treated with peginterferon alfa monotherapy. Regardless of genotype, individuals should be tested for viral load at 12 weeks, and if the viral load has reduced to less than 1% of its level at the start of treatment, treatment should be continued for a total of 48 weeks. If viral load has not fallen to this extent, treatment should stop at 12 weeks. 1.6 People for whom liver biopsy poses a substantial risk (such as those with haemophilia, or those who have experienced an adverse event after undergoing a previous liver biopsy), and

		people with symptoms of extra-hepatic HCV infection sufficient to impair quality of life, may be treated on clinical grounds without prior histological classification. 1.7 There is insufficient evidence to recommend combination therapy using peginterferon alfa or interferon alfa in people who: • are younger than 18 years of age, and/or • have had a liver transplantation. Treatment of CHC recurrence after liver transplantation (whether or not the person had been treated with interferon alfa or peginterferon alfa therapy at any time before transplantation) should be considered as experimental and carried out only in the context of a clinical trial.
ID654 - Sofosbuvir	Treatment of chronic hepatitis C	Ongoing technology appraisal
ID668 – Simeprevir	Treatment of chronic hepatitis C	Ongoing technology appraisal

In addition to the above, NICE has published the following public health guidance 'Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection'.18 This guidance provides recommendations covering:

- Awareness raising among the general population and people at increased risk of hepatitis B and C infection
- Developing the knowledge and skills of healthcare professionals and other providing services for people at increased risk of hepatitis or C infection
- Testing (in primary care, prisons and youth offender institutions, immigration removal centres, drug services and genitourinary medicine and sexual health clinics)
- Contact tracing
- Providing and auditing neonatal hepatitis B vaccination
- Commissioning hepatitis B and C testing and treatment services
- Laboratory services for hepatitis B and C testing

The guidance does not provide detail on treatments for hepatitis C which are covered by the above technology appraisals.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The current clinical pathway of care takes into account the European Association for the Study of the Liver (EASL) guidelines and NICE Technology Appraisals (TA75, 106, 200, 252 and 253).

The aim of treatment is to cure hepatitis C and prevent liver disease progression, HCC development, death and HCV transmission. The HCV genotype influences treatment decisions and also the likelihood of response to therapy.

NICE guidance on hepatitis C (TA75, TA106) recommends that standard treatment for the majority of people with CHC, regardless of disease severity, is combination therapy with ribavirin and either PegIFN alfa-2a or PegIFN alfa-2b. Monotherapy with PegIFN alfa-2a or PegIFN alfa-2b is recommended for patients who are unable to tolerate ribavirin or for whom ribavirin is contraindicated.

NICE guidance on hepatitis C (TA200) also recommends that people who have been previously treated with PegIFN alfa and ribavirin or with PegIFN alfa monotherapy have an option to receive further courses of PegIFN alfa and ribavirin. Shortened courses of combination therapy are also recommended as an option for certain patient subgroups.

For people with HCV genotype 1, who have not been previously treated or who have been previously treated, NICE guidance recommends telaprevir in combination with PegIFN + RBV (TA252)30 or boceprevir in combination with PegIFN + RBV (TA253).

For each of the above regimens regular monitoring of treatment efficacy based on repeated measurements of HCV RNA is required in order to guide treatment, which typically lasts between 24 and 48 weeks.

Furthermore, of the HCV GT1 patients taking PegIFN + RBV, sentinel surveillance data suggest that rates of SVR (estimated for people identified as undergoing a first course of treatment between 2009 and 2012), were 54% in those with genotype 1 and 69% in those with non-1 genotypes; and equivalent SVR rates for 2012 alone remained unchanged at 54% for GT1. [10] These data suggest that whilst these regimens are effective to a degree, there is a need for more efficacious treatments.

In 2014, two new agents simeprevir + PegIFN + RBV and sofosbuvir +/- PegIFN + RBV received marketing authorisations for the treatment of hepatitis C. At the time of writing this submission, NICE is in the process of developing technology appraisal guidance for these two agents – simeprevir ID668[19] and sofosbuvir ID654.[20] However, if recommended by NICE it is anticipated that these agents will be used either alongside or instead of telaprevir or boceprevir for GT1, and also instead of PegIFN + RBV for GT4.

AbbVie's 3D and 2D regimen

AbbVie's all-oral, Peg-IFN-free anti-viral combination offers a step change in the way chronic HCV GT1 and GT4 patients are treated. 3D and 2D have the potential to significantly improve patients' HRQoL by allowing greater numbers of patients, including those who are not eligible for or intolerant to the current regimens, to receive shorter, more efficacious and more tolerable therapy.

Given the well-documented and harmful side effects of interferon, its elimination from the treatment regimen represents a significant advance and step-change from the current interferon-based regimens. As mentioned above, interferon-based regimens have demonstrated poor tolerability and adherence, limiting their uptake and reducing the likelihood of achieving SVR.

AbbVie's regimens have demonstrated significant improvements in clinical efficacy, even in cirrhotic patients (SVR response rates following 12 weeks treatment of 3D +

RBV were 94.2% for treatment naïve cirrhotic GT1 patients and 90.2% for PegIFN/RBV treatment-experienced cirrhotic GT1 patients). Therefore by offering high probability of SVR even to the hardest to treat patients, AbbVie's HCV treatment regimens will reduce numbers of people living with preventable ill health, people dying prematurely due to liver disease, and may help reduce health inequalities and improve health overall especially amongst the most marginalised groups of our society.

It is expected that AbbVie's all-oral 3D and 2D regimens will replace the PegIFN containing regimens, removing the need for patients to self-inject interferon, for patients with HCV GT1 and GT4. For the significant proportion of patients who are unsuitable for interferon (either interferon-ineligible, intolerant or unwilling), AbbVie's 12 week regimens offer a highly effective treatment option for patients who would have otherwise had no recommended treatments available.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Current clinical practice of hepatitis C GT1 involves treatment with triple therapy (telaprevir and boceprevir in combination with PegIFN + RBV), and it is anticipated that simeprevir and sofosbuvir in combination with PegIFN + RBV may be used pending the outcome of NICE's ongoing technology appraisals for simeprevir and sofosbuvir.[19,20] Although chronic hepatitis C can be cured with effective treatment, there remains a significant unmet need with regards to treatment and the number of people who access it. Current treatment options can be successful and provide a cure for some patients, but they are not successful in a substantial proportion of people.[21] Limitations associated with the traditional treatments are discussed below. These limitations have left the majority of diagnosed patients without suitable treatment options. It is estimated that only 40% of HCV patients are considered eligible for treatment, hence there is a significant need for treatments which can be more widely used.[22]

Furthermore, the 2014 Public Health England report indicates that only 3% of patients with long-term infection start treatment each year.[10] Sentinel surveillance data suggest that rates of SVR (estimated for people identified as undergoing a first course of treatment between 2009 and 2012), were 54% in those with genotype 1 and 69% in those with non-1 genotypes; and equivalent SVR rates for 2012 alone remained unchanged at 54% for GT1. [10] This is particularly important considering that the PIs telaprevir and boceprevir were introduced in 2011.

For those PegIFN/RBV treated patients who do not achieve a SVR, retreatment with PegIFN/RBV is not recommended, leaving such patients limited treatment options and at risk of long term complications of HCV infection. EASL guidance stresses that re-treatment should only be offered to patients who have an urgent indication for therapy, and/or if there is evidence of inadequate prior exposure to either PegIFN or RBV.[21] As mentioned previously, the current standard of care treatments are unsuitable for the significant proportion of patients who are unsuitable for interferon (either interferon-ineligible, intolerant or unwilling). A substantial proportion of patients with HCV remain untreated due to contraindications to interferon therapy such as hepatic decompensation, autoimmune disease and psychiatric illness.[23]

<u>Protease-based triple therapy:</u>

In patients infected with HCV GT1, whilst telaprevir or boceprevir in combination with PegIFN and ribavirin improve cure rates, and in some patients shorten overall treatment duration, they are associated with a number of disadvantages. These include an increase in potentially life-threatening side effects, a complicated treatment regimen (high pill burden, thrice daily dosing and the need for a high fat diet), high rates of discontinuations and association with a number of clinically significant drug interactions and emergence of drug-resistant variants.[24,25,26]

Triple therapy with both telaprevir and boceprevir is associated with an increase in adverse events over and above those seen with PegIFN + RBV alone including rash, anaemia, nausea, haemorrhoids, diarrhoea, pruritus, fatigue, dysguesia and vomiting. In addition to the common side effects of telaprevir (aforementioned), drug rash with eosinophilia and systemic symptoms (DRESS) and Steven Johnson syndrome (a life-threatening skin condition) may also be observed in some patients. A 'black box' warning for toxic epidermal necrosis, another life-threatening skin condition, associated with telaprevir therapy was announced by the FDA in 2012. For boceprevir, the most common side effects are anaemia, fatigue, nausea, headache, dysgeusia, dry mouth, vomiting and diarrhoea. These adverse events have a negative impact on adherence to, and tolerability of, these triple therapy regimens.

These regimens have also had limited success in patients with advanced liver fibrosis and in patients who have previously had only a partial response or not responded to peginterferon and ribavirin. These factors are especially relevant in view of the rising age of the HCV-infected population and the associated increase in the number of patients with advanced liver disease and previous treatment failure.

An additional limitation is the complexity of treatment regimens with telaprevir and boceprevir (e.g. the need for lead-in treatment or extended treatment with PegIFN + ribavirin depending on response) and the need for response guided therapy. Overall, the total length of treatment with telaprevir and boceprevir-based triple therapy ranges between 24 and 48 weeks, depending on baseline factors (e.g. cirrhosis), prior treatment history and on-treatment virological response. Both telaprevir and boceprevir are substrates and inhibitors of the hepatic enzyme cytochrome P4503A and the drug transporter, P-glycoprotein, which predisposes them to a wide range of drug–drug interactions. Interactions with drugs such as immunosuppressants and anti-retrovirals mean that the combination of such agents with either drug should be avoided or only considered with caution in special populations such as liver transplant recipients and HCV/HIV co-infected patients. [27]

Simeprevir licensed in mid-2014 demonstrates an improved adverse effect profile over the first generation PIs with a less burdensome regimen; however it still requires co-administration with PegIFN + RBV for HCV GT1 and an additional test for virologic resistance before administration. At the time of writing this submission, expert clinical advice given to AbbVie suggests that simeprevir is not yet considered a new standard of care and there is little or no usage of simeprevir according to available pharmaceutical company, pharmacy purchasing and pharmacy prescribing data which records amounts and use of prescribed medicines for chronic HCV in the UK.

<u>NS5B polymerase inhibitor:</u>

The NS5B polymerase inhibitor, sofosbuvir, was licensed in early 2014 in combination with PegIFN + RBV. Whilst sofosbuvir offers the potential for improved SVR rates and has a better adverse effect profile over the currently available PIs, it still requires co-administration with PegIFN + RBV. In its preliminary recommendations, 24 weeks of sofosbuvir + RBV is not recommended because it is

not a cost-effective use of NHS resources. As such, the NICE recommended sofosbuvir containing regimen still includes PegIFN and its treatment-limiting associated side effects. These include influenza-like symptoms, fatigue, depression, skin reactions and haematological events (anaemia, thrombocytopenia and neutropenia).[21]

Furthermore, Peg-IFN is absolutely contraindicated in a significant proportion of patients, including: patients with uncontrolled depression, psychosis or epilepsy; patients with uncontrolled autoimmune diseases; pregnant women or couples unwilling to comply with adequate contraception; patients with severe concurrent medical disease, such as poorly controlled hypertension, heart failure, poorly controlled diabetes, and chronic obstructive pulmonary disease.[21] Medical ineligibility, predominantly substance use disorders, psychiatric disorders and medical comorbidities, along with patient attitudes and preferences, are the most commonly cited barriers to treatment in HCV-infected patients.[22]

To conclude, there is a clear medical need for new treatments that don't require co-administration with PegIFN, which provide a shorter, simpler, better tolerated and more effective regimen with a high likelihood of success, which can be used for the treatment of naïve and treatment experienced patients with hepatitis C including those unsuitable for PegIFN.

2.7 Please identify the main comparator(s) and justify their selection.

HCV GT1

AbbVie considers that the main comparators for HCV GT1 are as follows:

- Telaprevir + PegIFN + RBV
- Boceprevir + PegIFN + RBV
- Simeprevir + PegIFN + RBV*
- Sofosbuvir + PegIFN + RBV
- Best supportive care for PegIFN ineligible/intolerant patients

Boceprevir + PegIFN + RBV and PegIFN + RBV are licensed for use in GT1 HCV patients who are eligible for PegIFN, but according to expert clinical advice and available pharmaceutical company, pharmacy purchasing and pharmacy prescribing data which records amounts and use of prescribed medicines for chronic HCV in the UK they are not widely used for HCV GT1 in current clinical practice in the UK and therefore do not constitute standard of care. However, AbbVie has still presented data for 3D vs these agents in Section 7 where the evidence allows. Some data suggest that dual therapy is still used in some centres across England & Wales, in patients who are either contraindicated or who are unable to tolerate the adverse effects of the PI-based treatments, however with the rapid introduction of new therapies with considerably reduced side effect profiles it is unlikely that dual therapy comprising PegIFN + RBV will be used.

**Simeprevir + PegIFN + RBV:*

AbbVie would have liked to include simeprevir + PegIFN + RBV as a comparator for GT1, given that preliminary recommendations from NICE recommend simeprevir + PegIFN + RBV for HCV GT1.[19] However, the licence for simeprevir states that GT1a HCV patients with Q80K positive polymorphism should consider alternative therapy.

Having analysed the manufacturer's submission (MS) and the ERG report for simeprevir, AbbVie can only find data stratified by fibrosis status for the ITT population (Table 17, page 51 of MS), and not for people who are Q80K negative. AbbVie's economic model requires that data are stratified by fibrosis status. This is because it is well documented that the fibrosis status affects the probability of achieving and SVR for the PegIFN containing regimens, and therefore an overall SVR estimate may over- or underestimate a regimen depending on the percentage of cirrhotic patients included at baseline – particularly in analyses where there has been no adjustment for the presence of cirrhosis or other know prognostic factors affecting response.

For the MTC (Section 6.7 of the MS) the manufacturer included clinical data only for the sub-group of Q80K negative patients in their trials as per the licence, which is expected as NICE can only make recommendations within the licensed population. However, these data are listed as "NR" in the data outputs for the MTC for QUEST-1 and QUEST-2 where they would have been presented by fibrosis stage (Table 24 – page 74 MS, Table 27 – page 77 MS). Therefore, whilst simeprevir has been incorporated into the economic model treatment library – it is based on data for the ITT population as that was all that was available. As such no analyses of AbbVie's regimens vs. simeprevir have been presented in this submission because it would include data for an unlicensed population.

Peg-IFN ineligible/intolerant HCV GT1 patients:

For interferon-ineligible, intolerant or unwilling HCV GT1 patients, there are currently no NICE recommended treatment options. In the preliminary recommendations of the ACD2 for appraisal ID654, 24 weeks of sofosbuvir + RBV is not recommended for PegIFN ineligible, intolerant or unwilling patients.[20] Similarly, in its preliminary recommendations for the use of simeprevir + sofosbuvir, NICE has not recommended this treatment for PegIFN ineligible or intolerant HCV patients.[19]

Furthermore, the clinical trial supporting the use of simeprevir + sofosbuvir does not allow AbbVie to do comparisons of clinical and cost-effectiveness. The COSMOS study comprises two cohorts: – previous non-responders with METAVIR scores F0–F2 (cohort 1) and previous non-responders and treatment-naive patients with METAVIR scores F3–F4 (cohort 2).[28] Given that the structure of our model necessitates that cirrhotics (F4) are separated out from mild (F0-F1) and moderate (F2-F3) HCV for both treatment naïve and treatment experienced patients, it isn't possible to extrapolate the data from COSMOS to populate the model in this way.

Therefore, the comparator for PegIFN ineligible/intolerant patients is best supportive care.

HCV GT4

AbbVie considers that the main comparators for HCV GT4 are as follows:

- PegIFN + RBV
- Sofosbuvir + PegIFN + RBV
- Simeprevir + PegIFN + RBV
- Best supportive care for PegIFN ineligible/intolerant patients

In its preliminary recommendations in the ACD2, NICE currently does not recommend sofosbuvir + PegIFN + RBV for the treatment of patients with HCV GT4.

At the time of this submission, it is still not known whether sofosbuvir will be recommended for HCV GT4, however there has been a 4th committee meeting where an inequality issue was raised. Therefore, AbbVie considers that sofosbuvir might be recommended by NICE and has therefore added it as a comparator for this group of patients.

In its preliminary recommendations of simeprevir + PegIFN + RBV, NICE is 'minded not to recommend' this treatment regimen in GT4 patients. The Committee recommends that NICE requests a detailed rationale from the company about whether the clinical effectiveness in people with genotype 1 hepatitis C virus (HCV) can be generalised to people with genotype 4 HCV. Given that this preliminary recommendation is only a minded no, which may change based on the evidence provided by the manufacturer, AbbVie attempted to include simeprevir + PegIFN + RBV as a comparator in this submission. However, examination of the RESTORE clinical trial data evaluating simeprevir in HCV GT4 infected subjects, revealed that the trial is a mixture of treatment naïve and experienced, and cirrhotics patients (23% patients were cirrhotic). Unfortunately the data are not presented by both fibrosis status and cirrhotic status. Therefore, given the known impact cirrhosis has on the probability of achieving an SVR (see Section 6.6) and the fact that we could not separate the SVR data out by these sub-groups according to our model structure, AbbVie felt it would be an unfair analysis to compare simeprevir to 2D, when the 2D trial PEARL-I excluded cirrhotic patients.

Similarly to GT1, for interferon-ineligible, intolerant or unwilling HCV GT1 patients, there are currently no NICE recommended treatment options. In the preliminary recommendations of the ACD2 for appraisal ID654, 24 weeks of sofosbuvir + RBV is not recommended for PegIFN ineligible, intolerant or unwilling patients.[20] Similarly, in its preliminary recommendations for the use of simeprevir + sofosbuvir, NICE has not recommended this treatment for PegIFN ineligible or intolerant HCV patients.[19] Therefore, the comparator for PegIFN ineligible/intolerant patients is best supportive care.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

There are very few side effects specifically associated with AbbVie's 3D and 2D regimen. There have been some side effects reported that are associated with the use of 3D + RBV or 2D + RBV, which can be attributed to the known adverse reactions of ribavirin e.g. anaemia. Section 6.9 discusses adverse reactions in much more detail. However to summarise here, for the very small percentage (0.2%) with neutropenia or thrombocytopenia, and for the 4.3% of patients we have assumed in the economic model to have anaemia, pharmacological therapies may be prescribed to treat these adverse events e.g. filgrastim for neutropenia.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

AbbVie's regimens will be administered in an already established hepatitis C treatment pathway where the required clinical infrastructure is in place. No additional costs are associated with administration and as response guided therapy and 'stopping rules' associated with first generation DAAs are not required, it is anticipated that monitoring costs will be reduced. However, based on expert clinical advice AbbVie has conservatively added similar monitoring costs to its regimen, as it has to the PegIFN containing regimens in the economic model (see Section 7.5).

Furthermore, the shorter dosing schedules of AbbVie's regimens vs. the traditional PegIFN containing regimens, and the improved tolerability profile compared with current standard of care treatment (PegIFN + RBV containing regimens) may also reduce associated healthcare costs.

See Section 7.5 for further details on costs.

2.10 Does the technology require additional infrastructure to be put in place?

No. In contrast, AbbVie's regimens have a shorter treatment duration with considerably fewer side effects than the majority of PegIFN containing regimens; and the fact that response guided therapy and stopping rules are not required, means that the use of 3D and 2D may reduce pressures on the current infrastructure.

3 Equality

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology**
- **could lead to recommendations that have any adverse impact on people with a particular disability** or disabilities

Hepatitis C infection has a number of transmission routes of infection both for recent and past infections and affects a wide variety of people across society. Nevertheless there may be people who share population characteristics as defined in the Equality Act who fall within the patient population licensed for treatment. Furthermore, there may also be groups affected by health inequalities associated with socioeconomic inequalities that should be considered. For example, around half of those chronically infected with hepatitis C are in the lowest socio-economic quintile, and around three-quarters of those chronically infected are in the lowest two quintiles. Additionally, Public Health England estimates that the prevalence of hepatitis C within the prison estate is significantly higher than the general population (10% vs 0.4%). These groups are summarised below:

- Ethnic groups disproportionately affected by genotype 4 (equality legislation)
- HIV co-infected patients (equality legislation)
- Prison populations (health inequality)
- Homeless people (health inequality)

3.1.2 How has the analysis addressed these issues?

AbbVie has presented results for each of the subgroups outlined in the final scope document. However, it should be recognised that differential recommendations across different subgroups may lead to discrimination against groups protected by equality legislation. Genotype 4 infection predominantly affects people from North Africa, the Middle East and Central Africa with Egypt having a notably high genotype 4 prevalence. As such any recommendation that differs between genotype 1 and 4

will have a differential on migrants from countries with a high prevalence of genotype 4.

AbbVie notes that in consultation on the recommendations for sofosbuvir in combination with PegIFN/RBV that comments made by the National Aids Trust have highlighted that patients with HIV co-infection may be classified as disabled under the disability discrimination legislation. Section 6.5.1.9 shows that the efficacy of 3D does not differ in patients who are HIV co-infected, with SVR12 rates of 93.5% in HCV/HIV-1 co-infected patients receiving 3D + RBV for 12 weeks. In addition, expert clinical advice suggests that for people infected with both HCV and HIV, successful treatment of HCV can have a beneficial effect on the treatment of HIV. Therefore, AbbVie considers that recommendations should be applicable for all patients regardless of HIV co-infection status.

The prevalence of HCV infection is higher in prison populations and among people who are homeless than in the general population. One of the benefits of providing these people with an effective well tolerated, all-ora, treatment option would be to reduce health inequality among these groups versus the general population, alongside the benefit of reducing onward transmission of infection.

Finally, it is important to consider the equality of opportunity for patients who are classified as cirrhotic versus non-cirrhotic. Patients can be misclassified as being F3 when they are F4 therefore AbbVie considers that differential recommendations should not be made between cirrhotic and non-cirrhotic subgroups.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

The 3D regimen for genotype 1 patients and the 2D regimen for genotype 4 patients should be considered a step change in the treatment of hepatitis C compared to current standard of care. These interferon-free regimens have the benefits of being all oral therapies with a dramatically improved tolerability and efficacy profile and significantly shorter treatment durations versus existing interferon containing regimens.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

The most important significant and substantial health-related benefit that is unlikely to be captured in the QALY calculation is the prevention of onward transmission of HCV. This means that the use of the 3D and 2D regimens will be more cost effective than shown using the cost per QALY calculations excluding these transmission benefits. Effective treatment of patients with HCV will reduce the demand for liver transplants so use of the 3D and 2D regimens could have a positive impact on reducing the waiting list for liver transplants. The requirement for liver transplantation is expected to increase over time in the UK due to HCV and alcoholic liver disease. This pressure will continue unless these preventable diseases can be reduced because the supply of donors is not increasing at the same rate. The opportunity cost of current HCV treatment rates on the liver transplant waiting list is not captured in the cost per QALY assessment.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

The potential of AbbVie's 3D and 2D regimen to make a significant and substantial impact on health-related benefits is evidenced by the EMA and FDA permitting the use of historical control trials to facilitate an expedited clinical trial programme and granting the 3D regimen an accelerated regulatory approval process. The EMA process is only available for medicines expected to have a significant impact on public health.

Martin *et al*. have modelled the benefits of interferon-free regimens for reducing onward transmission and reducing the prevalence of HCV. [29]

Flemming *et al.* have assessed the impact of HCV infection on the demand for liver transplantation in the US. The authors concluded 'Looking to the future, the demand for liver transplantation for HCC will likely continue to rise and further strain the limited donor pool'. [30]

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with chronic hepatitis C (CHC): • 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 CHC genotype 1 and genotype 4: • who have not had treatment for chronic hepatitis C before (treatment-naive) • who have had treatment for chronic hepatitis C before (treatment-experienced)	As specified in the scope, but more specific to be in line with the licence. I.e. specifically for adults with CHC genotype 1 or genotype 4.
Intervention	Co-formulated ombitasvir/paritaprevir/ritonavir with (3D) or without dasabuvir (2D), co-administered with or without ribavirin	Co-formulated ombitasvir/paritaprevir/ritonavir with (3D) or without dasabuvir (2D), co-administered with or without ribavirin	As specified in the scope.
Comparator(s)	The scope lists the following comparators: • PegIFN/RBV (genotypes 1-6) • Telaprevir + PegIFN/RBV (for genotype 1 only) • Boceprevir + PegIFN/RBV (for genotype 1 only) • Sofosbuvir + RBV, with or without PegIFN (genotypes 1-6) (subject to ongoing NICE appraisal ID654) • Simeprevir + PegIFN/RBV (genotype 1 or 4) (subject to ongoing NICE appraisal ID668) • Simeprevir + sofosbuvir +/-, with or without ribavirin (for people who have genotype 1 or 4 disease and are ineligible for or intolerant to interferon treatment) (subject to ongoing NICE appraisal ID668) • Best supportive care (watchful waiting) (genotypes 1-6)	Where the data allows AbbVie has performed comparisons in line with the licence for 3D and 2D with the comparator agents listed in the final scope. Note, where certain combinations are not recommended by NICE or where the evidence does not allow for a comparison, no analyses have been performed. Details of all the comparator analyses that were possible are discussed in Section 2.7 and 7.3.1.	As per scope where data allows.

Outcomes	The outcome measures to be considered include: • SVR • development of resistance to 3D or 2D therapy • mortality • adverse effects of treatment • Health-related quality of life.	The outcome measures included in the decision problem are: • SVR12 • development of resistance to 3D or 2D therapy • mortality • adverse effects of treatment • Health-related quality of life.	As specified in the scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	• Cost-effectiveness will be presented as incremental cost per quality adjusted life-year (QALY). • The time horizon for the modelling is a lifetime. • Costs will be considered from an NHS and Personal Social Services perspective.	As specified in the scope.
Subgroups to be considered	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	As per scope. Note, given that SVR data are similar for HCV mono-infection and HCV/HIV co-infection, the clinical data are presented in the submission, but the modelling for HCV infection is assumed to be the same if a person was co-infected. i.e. HIV co-infection is not modelled as a

			separate sub-group.
Special considerations, including issues related to equity or equality	None stated.	HCV may affect certain groups that fall under the Equality Act: • Ethnic groups disproportionately affected by genotype 4 (equality legislation) • HIV co-infected patients (equality legislation) • Prison populations (health inequality) • Homeless people (health inequality)	None identified in the scope but there may be special considerations for some patient populations the Committee might want to consider.

Section B – Clinical and cost effectiveness

6 Clinical evidence

6.1 Identification of studies

6.1.1 **Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.**

As discussed in Section A, AbbVie's regimens for hepatitis C infection comprise either ombitasvir/paritaprevir/ritonavir with dasabuvir for HCV genotype 1 or ombitasvir/paritaprevir/ritonavir HCV for genotype 4. A systematic review was carried out to identify all the relevant trials of these regimens for the treatment of hepatitis C. Full details of the search strategies are provided in Appendix 2, Section 10.2.

Databases searched include:

- BIOSIS Previews ®
- Excerpta Medica Database (EMBASE®)
- EMBASE® Alert
- MEDLINE®
- SciSearch®
- Current Contents Search®
- Derwent Drug File

In addition, the Clinical Study Reports (CSRs) were available for each of the identified trials where published information on the trials was limited. To be included in the review trials had to meet pre-defined eligibility criteria, which are outlined in Table 23. Implementation and reporting of the systematic review followed the recommendations and standards required by NICE and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Citations were first screened based on the title and abstract supplied with each citation. Citations that did not match the eligibility criteria were excluded at this point, and where unclear, citations were included. In any case, all the citations (both included and excluded) retrieved following the search strategy are included in Appendix 2 to enable the reviewers to see what citations were excluded at the 'first pass'. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded and full-text copies of all references that could potentially meet the eligibility criteria were ordered at this stage. Following this, the eligibility criteria were applied

to full-text citations. Each full text article was screened by an independent reviewer. If more than one publication describing a single trial was identified, the data was compiled into a single entry in the data extraction table to avoid double counting – whoever this was not the case for AbbVie's regimens.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table 23: Eligibility criteria used in search strategy

Inclusion criteria	Details	Comments
Patient population	Chronic hepatitis C patients (genotype 1 or genotype 4)	In line with the scope
Intervention	3D or 2D	Search strategy included the INN names as well as other acronyms of AbbVie's regimens
Comparators	Any	
Outcomes	SVR12, SVR24	Sustained virologic response (SVR): absolute number or percentage for SVR 12 and/or 24 weeks after end of treatment
Study type	All phase II/III clinical trials	All RCTs, as well as including single-blinded or open-label studies
Publication type	Full-text journal publications that are available; abstracts that report SVR12 or SVR24	
Language restrictions	English only	

Exclusion criteria	Details	Comments
Patient population	Not patients with HCV genotype 1 or 4 – i.e. HCV patients with other genotypes (2,3,5 or 6)	In line with the scope and the proposed licence
Intervention	Not a trial of the proposed licensed regimen	For example trials of 2D in HCV patients with genotype 1.
Comparators	No exclusions	
Outcomes	Studies that do not report SVR	
Study type	Not a clinical trial in humans	E.g. Excluded studies include pharmacokinetic studies, in vitro studies, animal studies
Publication type	Not publication of RCT (e.g., review, letter, commentary)	

Language restrictions	Not English	

6.2.2 **A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.**

All studies identified in the literature were AbbVie sponsored studies. All the citations identified in the literature review are included in Appendix 10.2. Searching ClinicalTrials.gov shows that all the trials are AbbVie funded and as such there is no need to identify further data sources to support the evidence base, as all the clinical trials have been included in this submission. Therefore, AbbVie has not provided a flow diagram of the numbers of studies included and excluded at each stage, but this can be calculated from the search strategy and the citations in Appendix 10.2 if need be.

6.2.3 **When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.**

Not applicable.

Complete list of relevant RCTs

6.2.4 **Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.**

AbbVie's HCV regimens have been studied in an extensive clinical trial programme in over 2,000 chronic HCV patients including a number of study sites in the UK. Patient populations studied included HCV treatment-naïve and Peg-IFN + RBV treatment-experienced patients, and those with characteristics that have historically been associated with poor response to treatment such as cirrhosis, older age, and high baseline HCV viral loads. Figure 4 gives a schematic overview of the AbbVie clinical trial evidence base provided to EMA and Table 24 and Table 25 provide more information about the trials.

Two phase II studies – AVIATOR and M14-103 were included in the EMA filing as supplementary information. They have been included within this submission for completeness, but AbbVie has not provided as much detail for these studies as it has for the pivotal studies - as these phase II studies are not used in the economic model and do not form part of the pivotal trials of the EMA regulatory submission.

In addition, two studies – TURQUOISE-I (evaluating 3D + RBV in HCV GT1 patients co-infected with HIV-1) and M12-999 (evaluating 3D +/- RBV in HCV GT1 patients post-transplant) are currently ongoing and are not due to complete until May 2016 and February 2016 respectively. However, preliminary results have been included in this submission as preliminary data have been provided to EMA to support the regulatory filing. Unfortunately, it is not possible to provide all the methodology required as the trials have not completed; AbbVie has provided as much information as possible about these trials in Section 6.5.

Figure 4: Overview of the completed AbbVie phase II/III HCV clinical trial programme submitted to EMA

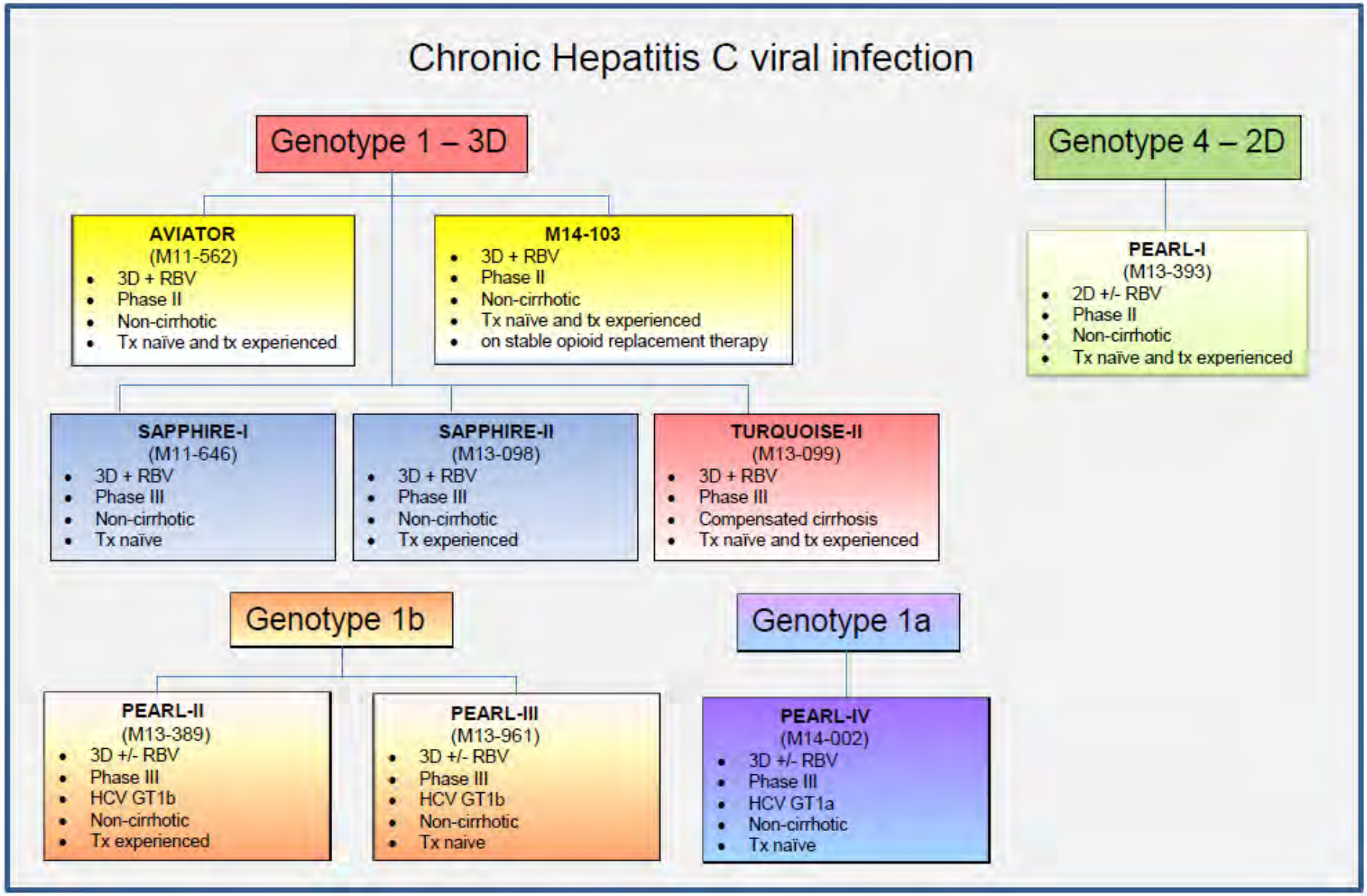


Table 24 – List of relevant RCTs for 3D (ombitasvir/paritaprevir/ritonavir and dasabuvir) for HCV genotype 1

Trial no. (acronym)	Intervention/ Duration of treatment	Comparator	Population	Primary study ref.
M11-646 (SAPPHIRE-I) Phase III	• **3D + RBV** (25 mg ombitasvir/ 150mg paritaprevir/100mg ritonavir and 500mg dasabuvir) in combination with ribavirin • 12 weeks	Historical SVR rate for telaprevir + pegIFN+RBV	• HCV GT1 • non-cirrhotic • treatment naïve • n=636	Feld *et al*, 2014[31]
M13-098 (SAPPHIRE-II) Phase III	• **3D + RBV** (25 mg ombitasvir/ 150mg paritaprevir/100mg ritonavir and 500mg dasabuvir) in combination with ribavirin • 12 weeks	Historical SVR rate for telaprevir + pegIFN+RBV	• HCV GT1 • non-cirrhotic • PegIFN/RBV treatment-experienced • n=395	Zeuzem *et al,* 2014[32]
M13-099 (TURQUOISE-II) Phase III	• **3D + RBV** (25 mg ombitasvir/ 150mg paritaprevir/100mg ritonavir and 500mg dasabuvir) in combination with ribavirin • 12 and 24 weeks	Historical SVR rate for telaprevir + pegIFN+RBV	• HCV GT1 • compensated cirrhosis • treatment naïve and pegIFN/RBV treatment-experienced • n=381	Poordad *et al*, 2014[33]
M13-389 (PEARL-II) Phase III	• **3D +/- RBV** (25 mg ombitasvir/ 150mg paritaprevir/100mg ritonavir and 500mg dasabuvir) with and without ribavirin • 12 weeks	Historical SVR rate for telaprevir + pegIFN+RBV	• HCV Gt1b • Non-cirrhotic • pegIFN/RBV treatment-experienced • n=187	Andreone *et al*, 2014[34]
M13-961 (PEARL-III) Phase III	• **3D +/- RBV** (25 mg ombitasvir/ 150mg paritaprevir/100mg ritonavir and 500mg dasabuvir) with and	Historical SVR rate for telaprevir + pegIFN+RBV	• HCV GT1b • non-cirrhotic • treatment naïve	Ferenci *et al*, 2014[35]

	without ribavirin • 12 weeks		• n=419	
M14-002 (PEARL-IV) Phase III	• **3D +/- RBV** (25 mg ombitasvir/ 150mg paritaprevir/100mg ritonavir and 500mg dasabuvir) with and without ribavirin • 12 weeks	Historical SVR rate for telaprevir + pegIFN+RBV	• HCV GT1a • non-cirrhotic • treatment naïve • n=305	Ferenci *et al*, 2014[35]
M11-652 (AVIATOR) Phase II – dose finding	• **3D + RBV** (ombitasvir/ paritaprevir/ ritonavir and dasabuvir) in combination with ribavirin - multiple dosing regimens • 8, 12 and 24 weeks	None	• HCV GT1 • non-cirrhotic • treatment naïve and previous null responders to PegIFN/RBV • n=580	Kowdley *et al*, 2014[36]
M14-103 Phase II	• **3D + RBV** (25 mg ombitasvir/ 150mg paritaprevir/100mg ritonavir and 500mg dasabuvir) in combination with ribavirin • 12 weeks	None	• HCV GT1 • non-cirrhotic • treatment naïve and PegIFN/RBV treatment-experienced • on stable opioid replacement therapy • n=38	None as yet.[37] Submitted to Journal of Hepatology.

White cells delineate pivotal data; greyed out cells indicate supplementary data for EMA submission

Table 25 – List of relevant RCTs for 2D (ombitasvir/paritaprevir/ritonavir) for HCV genotype 4

Trial no. (acronym)	Intervention/ Duration of treatment	Comparator	Population	Primary study ref.
M13-393 (PEARL-I) Phase II	• **2D +/- RBV** (25 mg ombitasvir/ 150mg paritaprevir/100mg ritonavir) with and without ribavirin • 12 weeks	None	• HCV GT4 • non-cirrhotic • treatment naïve and PegIFN/RBV treatment-experienced • n=86	Hezode *et al* 2014.[38] Pol *et al*

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

For HCV genotype 1, whilst none of the trials in Table 24 directly compare AbbVie's regimens with the comparators listed in the final scope, all the trials were powered to detect superiority of efficacy vs. telaprevir + PegIFN/RBV – one of the listed comparators in the decision problem. The trials were designed in conjunction with EMA and the US FDA where it was deemed that comparisons vs. historical cohorts of telaprevir were sufficient to demonstrate efficacy. AbbVie's clinical trials were therefore powered to detect inferiority and subsequent superiority vs. historical telaprevir SVR rates in similar populations.

Both SAPPHIRE-I and SAPPHIRE-II contained a placebo-controlled period in the trial designs, however this was to identify any differences in adverse events between AbbVie's regimen and placebo. Following 12 weeks of placebo, patients in the placebo arms of the SAPPHIRE studies immediately received 12 weeks of 3D and were assessed for SVR response 12 weeks after the end-of-treatment. As such, no efficacy outcomes were collected in the 12 week placebo-controlled period of the trials.

For HCV genotype 4, none of the trials in Table 25 compare AbbVie's regimens with the comparators listed in the final scope.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

As mentioned above, two phase II studies – AVIATOR and M14-103 were included in the EMA filing as supplementary information for patients with HCV GT1. They have been included within this submission for completeness, but AbbVie has not provided as much detail for these studies as it has for the pivotal studies - as these phase II studies are not used in the economic model and do not form part of the pivotal trials for the EMA regulatory submission.

The phase II study PEARL-I (M13-393) had two primary objectives. The first objective was to assess the safety and efficacy (percentage of SVR12 responders) of 2D with or without ribavirin in treatment naïve and PegIFN/RBV treatment experienced HCV GT4-infected subjects, which has been included in this submission. The second objective was to assess the safety and efficacy (the percentage of subjects with SVR12) among treatment-naïve and prior PegIFN/RBV null responder HCV sub-genotype 1b (GT1b)-infected subjects without cirrhosis and

among treatment-naïve and PegIFN/RBV treatment-experienced HCV GT1b-infected subjects with compensated cirrhosis treated with 2D. All arms in PEARL-I evaluating 2D in GT1b patients have been excluded from further discussion in this submission because it is outside the proposed licence.

Please note that there are a number of phase II trials evaluating different combinations and different treatment duration of the directly acting antiviral agents (see https://clinicaltrials.gov/ct2/results?term=abt-450&recr=&rslt=&type=&cond=&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&gndr=&phase=1&rcv_s=&rcv_e=&lup_s=&lup e.g. paritaprevir + dasabuvir, or ombitasvir + RBV. None of these trials have been included in the submissopm because they are not relevant to the decision problem as they are not the licensed regimen.

List of relevant non-RCTs

6.2.7 **Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.**

Not applicable.

6.3 *Summary of methodology of relevant RCTs*

6.3.1 **As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org).**

Summary methodology for the phase II (AVIATOR and M14-103) and pivotal phase III AbbVie clinical trials (SAPPHIRE-I, SAPPHIRE-II, TURQUOISE-II, PEARL-II, PEARL-III and PEARL-IV) for HCV GT1 have been provided in Table 7 to Table 11 (Section 6.3.2). In addition, methodology for the phase II trial PEARL-I in HCV GT4 subjects has been presented in Table 12.

The phase II trial AVIATOR and the following phase III trials (SAPPHIRE-I, SAPPHIRE-II, TURQUOISE-II, PEARL-III and PEARL-IV) have been published in the New England Journal of Medicine.[31,32,33,35,36] PEARL-II has been published in Gastroenterology. [34] M14-103 has been submitted to the Journal of Hepatology. Results from PEARL-I in HCV GT4 patients were presented at EASL in April 2014,[38] and the final CSR clinical study report is due October 2014. The CSRs for each study have been used as a source for additional information where necessary.

Methods

6.3.2 **Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.**

There are two phase II trials and six phase III trials evaluating AbbVie's 3D regimen in HCV GT1, including treatment naïve, treatment-experienced and compensated cirrhotic patients. In addition, there is one phase II trial evaluating 2D in treatment naïve and PegIFN/RBV treatment experienced HCV GT4 patients. The following tables describe the RCT's design and interventions, including details regarding length of follow-up and timing of assessments:

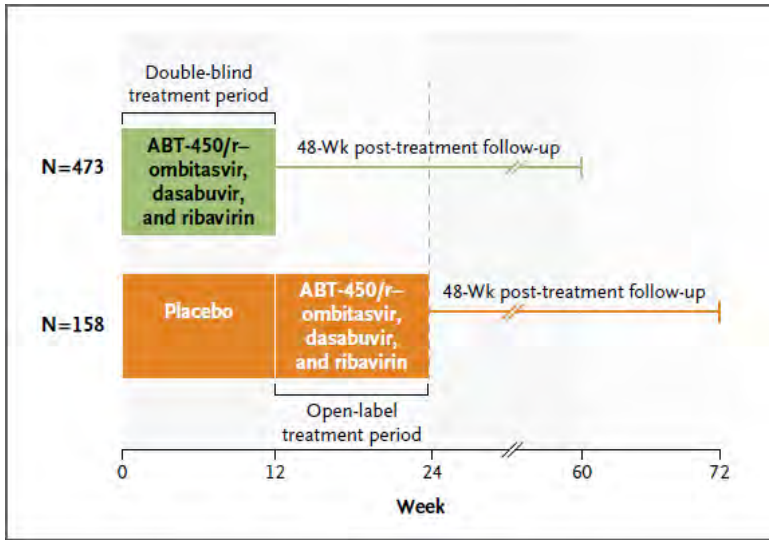
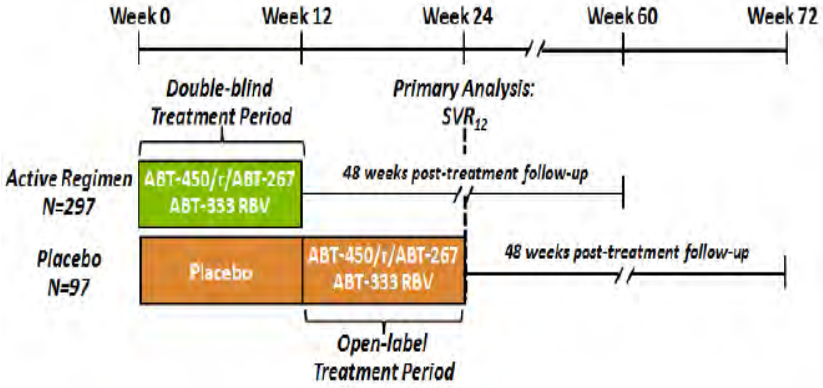
- Table 26 summarises the methodology for the SAPPHIRE trials in HCV GT1 treatment naïve (SAPPHIRE-I) and HCV GT1 PegIFN/RBV treatment experienced (SAPPHIRE-II) patients.
- Table 27 summarises the methodology for TURQUOISE-II, an RCT evaluating 3D + RBV in treatment naïve or treatment experienced cirrhotic patients.
- Table 28 summarises the design etc. for PEARL-II (treatment-experienced) and PEARL-III (treatment naïve) HCV GT1b patients.

- Table 29 summarises the methodology for PEARL-IV, an RCT in treatment naïve HCV GT1a patients.

- Table 30 summarises the design etc. for the two phase II studies, AVIATOR and M14-103 in HCV GT1 patients.

- Table 31 summarises the methodology for PEARL-I, a phase II trial evaluating 2D in HCV GT4 treatment naïve and treatment experienced patients.

Table 26: Summary of methodology for the SAPPHIRE trials

Trial no. (acronym)	SAPPHIRE-I (M11-646)[31] Treatment naïve HCV GT1	SAPPHIRE-II (M13-098)[32] PegIFN/RBV treatment-experienced HCV GT1
Location	79 sites in North America, Europe, and Australia.	76 sites in Australia, North America and Europe
Design	Multicentre, randomised, placebo-controlled phase III study. Patients were randomly assigned in a 3:1 ratio to receive active treatment (group A) or placebo (group B). Randomisation was stratified according to HCV genotype (1a vs. non-1a) and IL28B genotype (CC vs. non-CC).  During the 12-week double-blind period, patients received either 3D (group A) or matching placebos (group B).	Multicentre, randomised, placebo-controlled phase III study. Patients were randomly assigned in a 3:1 ratio to receive an active regimen or placebo. Randomisation was stratified according to the type of response to previous PegIFN/RBV treatment (relapse, partial response, or null response) and HCV genotype (1a or non-1a).  During the 12-week double-blind period, patients received either 3D with ribavirin or placebo. Patients receiving placebo during the double-blind period, were treated with the active regimen for 12 weeks in open-label fashion at the conclusion of double-blind period.

Design (contd)	Patients receiving placebo were treated with the active regimen for 12 weeks in an open-label fashion at the conclusion of the double-blind period. The dashed vertical line indicates the time point at which the primary analysis, which compared the rate of sustained virologic response at 12 weeks after the end of therapy in group A with the rate in a historical control group, was performed.[31]	
Duration of study	12 week treatment duration 48 week post-treatment follow-up	12 week treatment duration 48 week post-treatment follow-up
Method of randomisation	At the screening visit, patients were assigned a unique patient number through the use of Interactive Response Technology (IRT). For patients who did not meet the study selection criteria, the site personnel contacted the IRT system and identified the patient as a screen failure. Enrolled patients retained their patient number, assigned at the Screening Visit, throughout the study. For enrolment of eligible patients into the study, the site utilized the IRT system in order to receive unique study drug bottle/kit numbers and a unique randomisation number. The randomisation number was used only by the Sponsor for loading the treatment assignments into the database. The study drug kit numbers and randomisation numbers were assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department. Contact information and user guidelines for IRT use were provided to each site. Upon receipt of study drugs, the site acknowledged receipt in the IRT system.	Patients were randomised to ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + weight-based RBV or placebo for 12 weeks in a 3:1 ratio at the start of the study on double-blind Day 1. The randomisation schedule was stratified by type of response to previous PegIFN/RBV treatment (null responder, partial responder, or relapser) and HCV sub-genotype (1a versus non-1a). The number of relapsers to previous PegIFN/RBV treatment was limited to ≤ 120 patients. The total number of partial responders plus relapsers to previous PegIFN/RBV treatment was limited to ≤ 300 patients to ensure adequate representation in the presumed harder to treat null-responder population (defined as < 1 log10 IU/mL HCV RNA reduction at Week 4 in patients who received at least 4 weeks of PegIFN/RBV). At the screening visit, patients were assigned a unique patient number through the use of IRT. For patients who did not meet the study selection criteria, the site personnel contacted the IRT system and identified the patient as a screen failure.

Method of randomisation (contd)		Enrolled patients retained their patient number, assigned at the Screening Visit, throughout the study. For enrolment of eligible patients into the study, the site utilized the IRT system in order to receive unique study drug bottle/kit numbers and a unique randomization number. The randomisation number was used only by the Sponsor for loading the treatment assignments into the database. The study drug kit numbers and randomization numbers were assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department. Contact information and user guidelines for IRT use were provided to each site. Upon receipt of study drugs, the site acknowledged receipt in the IRT system.
Method of blinding (care provider, patient and outcome assessor)	During the double-blind Treatment Period, measures to prevent implicit unblinding by laboratory results were used. Specifically, the results of HCV RNA, haemoglobin, haematocrit, ALT, AST, bilirubin (indirect and total), were blinded to the investigator, patient and Sponsor until the double-blind week 12 or premature discontinuation visit, unless criteria for virologic failure or relevant predefined toxicity were met, in which case the relevant laboratory data were unblended to the investigator, patient, and Sponsor.	During the 12 week double-blind treatment period, AbbVie, investigators, and subjects were blinded to drug assignment and virologic results for the duration of the DB Treatment Period. Virologic results were reviewed and virologic failure criteria were applied to those subjects randomised to active drugs by an unblended independent reviewer. Certain safety laboratory results which, if available, could have potentially been unblinded (such as haemoglobin, haematocrit, AST, ALT, and total and indirect bilirubin) were also blinded to AbbVie, investigators, and subjects. For each of the blinded laboratory tests, if a pre-specified toxicity threshold was exceeded, the relevant unblinded laboratory data were provided to the investigator and AbbVie. In addition, a subject's study drug assignment may have been unblinded (i.e., the laboratory results were provided to AbbVie and investigators), as directed by the toxicity management guidelines or at the investigator's discretion, if deemed necessary for subject safety.

Intervention(s) (n =) and comparator(s) (n =)	**Intervention**: **3D n= 473** once-daily dose of 150 mg ABT-450, 100 mg ritonavir, 25 mg of ombitasvir and dasabuvir (at a dose of 250 mg twice daily) with ribavirin, administered twice daily in a dose that was determined according to body weight (1000 mg daily if the body weight was <75 kg and 1200 mg daily if the body weight was ≥75 kg. **Comparator: placebo n=158**	**Intervention**: **3D n= 297** once-daily dose of 150 mg ABT-450, 100 mg ritonavir, 25 mg of ombitasvir and dasabuvir (at a dose of 250 mg twice daily) with ribavirin, administered twice daily in a dose that was determined according to body weight (1000 mg daily if the body weight was <75 kg and 1200 mg daily if the body weight was ≥75 kg. **Comparator: placebo n=97**
Primary outcomes	The primary efficacy end point was a sustained virologic response (i.e., an HCV RNA level of <25 IU per millilitre 12 weeks after the end of study treatment).	The primary efficacy end point was a sustained virologic response (i.e., an HCV RNA level of <25 IU per millilitre 12 weeks after the end of study treatment).
Secondary outcomes	Pre-specified secondary outcomes were: • Normalisation of the alanine aminotransferase level, • SVR at post-treatment week 12 according to HCV genotype (1a or 1b), • virologic failure during treatment, and • post-treatment relapse.	Pre-specified secondary outcomes were: • Normalisation of the alanine aminotransferase level, • SVR at post-treatment week 12 according to HCV genotype (1a or 1b), • virologic failure during treatment, and • post-treatment relapse.
Statistical analysis	The primary efficacy analyses assessed non-inferiority and superiority with respect to the rate of sustained virologic response at post-treatment week 12 associated with 3D + RBV by comparing it with a calculated historical control rate of 78% (95% confidence interval [CI], 75 to 80). This control rate was based on response rates among previously untreated patients without cirrhosis who received telaprevir and PegIFN/RBV – i.e. a similar patient population to SAPPHIRE-I (Feld *et al* supplementary appendix):	The primary efficacy analyses assessed the non-inferiority and superiority of the rate of sustained virologic response at post-treatment week 12 with 3D + RBV as compared with a calculated historical control rate of 65% (95% confidence interval [CI], 60 to 70). This control rate was based on response rates among patients with HCV genotype 1 infection and no cirrhosis who had previously been treated with PegIFN/RBV and who received retreatment with telaprevir and PegIFN/RBV – i.e. a similar patient population to SAPPHIRE-II. The control rate was weighted for the proportions of patients with a prior relapse, partial response, or null response that were expected in SAPPHIRE-II (Zeuzem *et al* supplementary appendix):

Statistical analysis (contd)

SVR Rates for Telaprevir-Based Therapy in Treatment-Naïve Subjects

Telaprevir Studies	ADVANCE T12/PR n/N (%)	ILLUMINATE T12/PR n/N (%)	Meta Analysis T12/PR % [95% CI]
Treatment-naïve subjects without cirrhosis[1]	270/342 (79)	367/479 (77)	78 [75, 80]
Treatment-naïve GT1a subjects	162/217 (75)	273/388 (70)	72 [68, 75]
Treatment-naïve GT1b subjects	119/142 (84)	112/149 (75)	80 [75, 84]

GT1a = genotype 1a; GT1b = genotype 1b

To establish that the rate of SVR at post-treatment week 12 associated with the active regimen was non-inferior to the historical control rate, the lower boundary of the 95% confidence interval for the rate of SVR at post-treatment week 12 in group A had to exceed the upper boundary of the 95% confidence interval for the control rate minus 10.5 percentage points (70%). To establish that the rate of sustained virologic response at post-treatment week 12 associated with the active regimen was superior to the historical control rate, the lower boundary of the 95% confidence interval for the rate in group A had to exceed the upper boundary of the confidence interval for the historical rate (80%). The two-sided 95% confidence intervals were calculated with the use of the normal approximation to the binomial distribution.

Analyses were performed in the modified intention-to-treat population, which included all the patients who underwent randomisation and received at least one dose of the study drug during the double-blind period. The primary analysis was performed after all the patients in group A reached post-treatment week 12 and all those in group B reached week 12 of open-label treatment.

Estimated SVR Rates for Telaprevir-Based Therapy in Treatment-Experienced, Without Cirrhosis

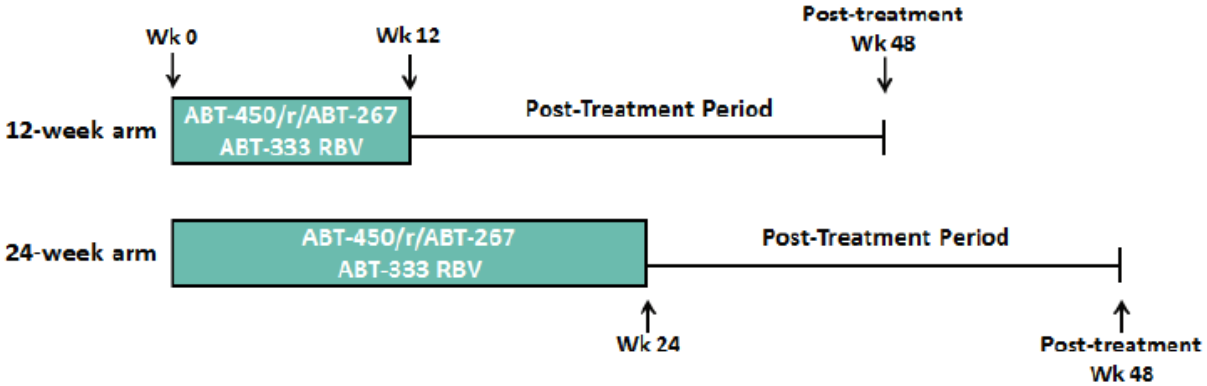
	REALIZE[4] All T12/P48[5] n/N (%)	REALIZE[4] Projected Enrollment in Study M13-098 (%)	REALIZE[4] Population-Based Weighted Average % [95% CI]
Prior relapsers	198/229 (86)	30	65 [60, 70]
Prior partial responders	46/65 (71)	35	
Prior null responders	40/97 (41)	35	

To establish that the rate of sustained virologic response with 3D + RBV was non-inferior to the historical rate, the lower boundary of the 95% confidence interval for the rate among patients receiving the active regimen during the double-blind period had to exceed the upper confidence boundary of the control rate minus 10.5 percentage points (60%). To establish that the rate of sustained virologic response with 3D + RBV was superior to the historical rate, the lower boundary of the 95% confidence interval for the rate among patients receiving the active regimen during the double-blind period had to exceed the upper confidence boundary of the historical rate (70%).

Analyses were performed in the modified intention-to-treat population, which included all the patients who underwent randomisation and received at least one dose of the study drug during the double-blind period.

Duration of follow-up	48 week post-treatment follow-up	48 week post-treatment follow-up

Table 27: Summary of methodology for TURQUOISE-II

Trial no. (acronym)	**TURQUOISE-II[33]** **HCV GT1 – compensated cirrhosis (tx naïve and tx-experienced)**
Location	78 sites in North America and Europe
Design	Phase III, multicentre, randomised, open-label trial. Patients were randomly assigned in a ratio of approximately 1:1 to the 12-week or 24-week treatment group, with stratification according to previous PegIFN/RBV treatment for HCV GT1 infection (no vs. yes). Previously untreated patients were stratified according to HCV sub-genotype (1a vs. 1b) and interleukin 28B (*IL28B*) genotype (CC vs. non-CC). Previously treated patients were stratified according to HCV sub-genotype and type of previous treatment failure: null response, partial response or relapse. Patients received 3D (at a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir and dasabuvir (250 mg twice daily) with ribavirin (1000 mg or 1200 mg daily, according to body weight, in two doses) for 12 weeks or 24 weeks. 
Duration of study	12 or 24 week treatment arms 48 week post-treatment follow-up

Method of randomisation	Patients were stratified by having received previous PegIFN/RBV treatment (treatment-experienced) versus being treatment-naïve. The treatment-naïve patients were stratified by HCV sub-genotype (1a versus non-1a) and by IL28B genotype (CC versus non-CC). The treatment-experienced patients were stratified by type of non-response to previous PegIFN/RBV treatment (null responder, partial responder, or relapser, as defined in the inclusion criteria) and by HCV sub-genotype (1a versus non-1a). Per the original protocol, the first 200 patients were randomised in a 3:5 ratio to the 12 and 24 week arms, and the last 100 patients were to be randomised in a 3:1 ratio to the 12- and 24-week arms to achieve an overall randomisation ratio of 1:1 to each arm.
Method of blinding (care provider, patient and outcome assessor)	Not applicable – open-label.
Intervention(s) (n =) and comparator(s) (n =)	**Intervention: 3D – 12 week group** n= 208 once-daily dose of 150 mg ABT-450, 100 mg ritonavir, 25 mg of ombitasvir and dasabuvir (at a dose of 250 mg twice daily) with ribavirin, administered twice daily in a dose that was determined according to body weight (1000 mg daily if the body weight was <75 kg and 1200 mg daily if the body weight was ≥75 kg. **Intervention: 3D – 24 week group** n= 172 once-daily dose of 150 mg ABT-450, 100 mg ritonavir, 25 mg of ombitasvir and dasabuvir (at a dose of 250 mg twice daily) with ribavirin, administered twice daily in a dose that was determined according to body weight (1000 mg daily if the body weight was <75 kg and 1200 mg daily if the body weight was ≥75 kg.
Primary outcome	The primary efficacy end point was a sustained virologic response (i.e., an HCV RNA level of <25 IU per millilitre 12 weeks after the end of study treatment). The primary study objectives were to assess the rate of sustained virologic response in the 12-week and 24-week groups for non-inferiority and superiority to a historical rate with telaprevir plus PegIFN/RBV among patients with HCV genotype 1 infection and cirrhosis (see statistical analysis below for further details on how this was calculated). All efficacy analyses were performed on the ITT population. HCV RNA levels were measured with the use of the

	COBAS TaqMan real-time reverse-transcriptase–polymerase-chain-reaction assay, version 2.0.
Secondary outcomes	The key secondary efficacy end point was the percentage of patients with a sustained virologic response in the 24-week group as compared with the 12-week group. Other secondary efficacy end points were the percentage of patients in each group with virologic failure during treatment or relapse after treatment. A gatekeeping multiple-testing procedure (described in the Poordad et al Supplementary Appendix) was used for the primary efficacy end point and the key secondary efficacy end point. Rates of virologic failure during treatment and relapse after treatment were not part of the multiple-testing procedure, because no hypothesis was being tested for those two end points. The rate of sustained virologic response at post-treatment week 12 was also determined for patient subgroups defined according to pre-specified baseline demographic or clinical characteristics. Virologic failure during treatment was defined as two consecutive HCV RNA measurements of more than 1 log10 IU per millilitre above the nadir at any time during treatment, an HCV RNA level of 25 IU per millilitre or more at all assessments during treatment among patients who received at least 6 weeks of treatment, or a confirmed HCV RNA level of 25 IU per millilitre or more after a level of less than 25 IU per millilitre during treatment. Virologic relapse was defined as a confirmed HCV RNA level of 25 IU per millilitre or more between the end of treatment and 12 weeks after the last dose of study drug among patients who completed treatment and had an HCV RNA level of less than 25 IU per millilitre at the final visit during the treatment period.
Statistical analysis	All efficacy analyses were performed on the ITT population. The overall 2-sided significance level of 0.05 was split between the 2 arms using a Bonferroni correction of 0.025 for each arm. The percentage of patients achieving SVR12 within each treatment arm was calculated and a 2-sided 97.5% CI of the percentage was computed using the normal approximation to the binomial distribution. Historical SVR24 rates for telaprevir plus PegIFN/RBV in HCV genotype 1, treatment-naïve or treatment-experienced subjects with cirrhosis from the ADVANCE, ILLUMINATE, and REALIZE trials are presented the tables below. A fixed-effect meta-analysis was used to calculate the estimated SVR rate and 95% confidence interval (CI) in the treatment-naïve population. A weighted average of the corresponding SVR rates among treatment-naïve and treatment-experienced (prior null responders, partial responders, and relapsers) subjects was calculated to reflect the population expected to enrol in TURQUOISE-II. For a regimen to be considered superior to the historical SVR rate for telaprevir plus PegIFN and RBV, the lower confidence bound (LCB) of the SVR rate for that regimen must exceed the upper confidence bound of the historical SVR rate for telaprevir plus PegIFN/RBV, presented in Table 2 (i.e., 54%). A non-inferiority margin of 10.5% for comparisons to the

historical SVR rate for telaprevir plus PegIFN/RBV was based on the telaprevir ILLUMINATE study, which used the same non-inferiority margin. Thus, to be considered non-inferior to the historical SVR rate for telaprevir, the lower bound of the 95% CI for the SVR rate must be greater than the upper confidence bound of the SVR rate for the telaprevir-based therapy, minus 10.5% (i.e., 43%).

Table S1. SVR Rates for Telaprevir plus PegIFN and RBV in HCV Genotype 1 Treatment-Naïve Subjects

	ADVANCE	ILLUMINATE	Meta Analysis
Telaprevir Studies	**T12/PR n/N (%)**	**T12/PR n/N (%)**	**T12/PR % [95% CI]**
Treatment-naïve subjects with cirrhosis	15/21 (71)	31/61 (51)	56 [45, 67]

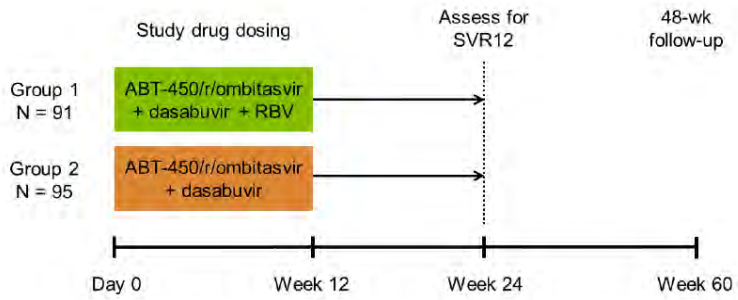
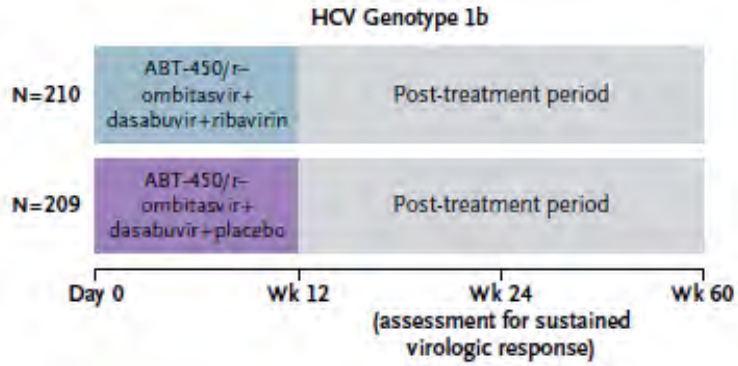
Table S2. Estimated SVR Rates for Telaprevir plus PegIFN and RBV in HCV Genotype 1 Cirrhotic Subjects

	REALIZE		
	Telaprevir-Treated Subjects with Cirrhosis n/N (%)	**Projected Enrollment in Study M13-099 (%)**	**Population-Based Weighted Average % [95% CI]**
Meta Analysis of ADVANCE and ILLUMINATE Studies (Table 1)			
Naïve Subjects	(56)	53	
REALIZE Study			
Prior relapsers	48/57 (84)	12	47 [41, 54]
Prior partial responders	11/32 (34)	12	
Prior null responders	7/50 (14)	23	

Analyses were performed on the modified intent-to-treat population (all randomly assigned patients who received at least one dose of study drugs). The 12-week and 24-week groups were compared with the use of a logistic-regression model, as pre-specified in the protocol for the key secondary efficacy end point, with treatment group, baseline log10 HCV RNA level, HCV sub-genotype (1a vs. 1b), *IL28B* genotype (CC vs. non-CC), and previous peg-interferon–ribavirin treatment (no vs. yes) as

	predictors of the rate of sustained virologic response at post-treatment week 12. Rates of sustained virologic response were summarized for each treatment group and randomization stratum to assess responses across stratification variables. For exploratory purposes, a stepwise logistic-regression model was used to assess the association between the rate of sustained virologic response at post-treatment week 12 and continuous and categorical subgroup variables. Statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute). All statistical tests and confidence intervals were two-sided, with a significance level of 0.05. The number and percentage of patients with adverse events, abnormalities in laboratory values of grade 3 or 4, or abnormalities in haemoglobin levels were compared between treatment groups with the use of Fisher's exact test.
Duration of follow-up	48 week post-treatment follow-up

Table 28: Summary of methodology for PEARL-II and PEARL-III (HCV GT1b)

Trial no. (acronym)	PEARL-II[34] HCV GT1b PegIFN/RBV treatment-experienced	PEARL-III[35] HCV GT1b treatment-naïve
Location	43 sites in Austria, Belgium, Italy, The Netherlands, Portugal, Puerto Rico, Sweden, Switzerland, Turkey, and the US.	50 sites in Austria, Belgium, Hungary, Israel, Italy, Poland, Portugal, Romania, the Russian-federation, Spain and the US.
Design	Phase III, multicentre, randomised, open-label trial. Patients were stratified by type of previous nonresponse to PegIFN/RBV treatment (null responders, partial responders, and relapsers) and randomised 1:1 to receive the 12-week regimen of co-formulated ABT-450/ritonavir/ombitasvir (150/100/25 mg once daily) and dasabuvir (250 mg twice daily) with either weight-based RBV dosed twice daily (1000 mg daily if body weight < 75 kg, 1200 mg daily if body weight was ≥ 75 kg) for group 1 or without RBV for group 2.  After 12 weeks treatment, patients were followed up for an additional 48 weeks.	Phase III, multicentre, randomised, double-blinded, placebo-controlled trial. Patients were stratified according to *IL28B* genotype (CC vs. non-CC) and randomly assigned in a 1:1 ratio to receive either ribavirin twice daily according to body weight (1000 mg daily if the body weight was <75 kg and 1200 mg daily if the body weight was ≥75 kg) or matching placebo for 12 weeks. All the patients received open-label ABT-450/r–ombitasvir (at a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir) and dasabuvir (250 mg twice daily) for 12 weeks:  Visits were scheduled at weeks 0, 1, 2, 4, 6, 8, 10, and 12 of

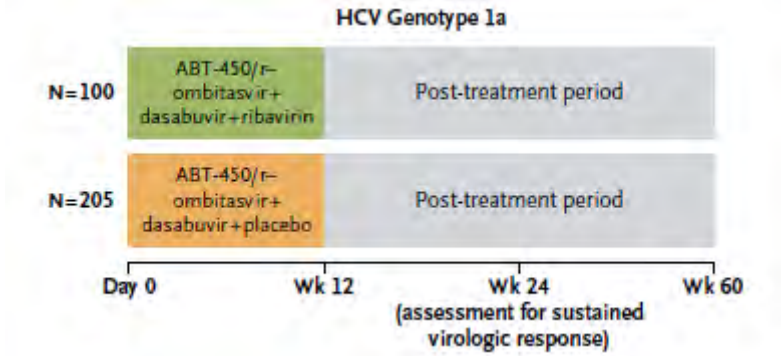
		the treatment period, and patients were followed for 48 weeks after the treatment period.
Duration of study	12 weeks treatment 48 week follow-up	12 week treatment period 48 week follow-up
Method of randomisation	Patients who met the eligibility criteria were enrolled via the Interactive Response Technology (IRT) system on Study Day 1. Prior to the study, contact information and user guidelines for the IRT system were provided to each site. For enrolment of eligible patients on Day 1, the site contacted the IRT system in order to receive a unique randomisation number and study drug kit numbers. The study drug kit numbers were assigned according to a randomization schedule computer generated before the start of the study by the AbbVie Statistics Department. Initial randomisation occurred in a 1:1 ratio to the two treatment groups. Randomisation of patients was stratified by the type of non-response to previous PegIFN/RBV treatment (null responders, non-responders/partial responders and relapsers). The number of non-responders/partial responders plus relapsers enrolled across Arms 1 and 2 was limited to 130 to ensure that at least 80 null responders were enrolled. In addition, the relapsers were limited to 60 patients (approximately 30% of all patients).	At the screening visit, patients were assigned a unique patient number through the use of Interactive Response Technology (IRT). For patients who did not meet the study selection criteria, the site personnel contacted the IRT system and identified the patient as a screen failure. Enrolled patients retained their patient number, assigned at the Screening Visit, throughout the study. For enrolment of eligible patients into the study, the site utilized the IRT system in order to receive unique study drug bottle/kit numbers and a unique randomisation number. The randomization number was used only by the Sponsor for loading the treatment assignments into the database. The study drug kit numbers and randomisation numbers were assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department. Contact information and user guidelines for IRT use were provided to each site. Upon receipt of study drugs, the site acknowledged receipt in the IRT system.
Method of blinding (care provider, patient and outcome assessor)	N/A - open-label.	Treatment assignment was to remain blinded to the investigator, patient, and sponsor. During the Treatment Period, ABT-450/r/ombitasvir and dasabuvir were provided as tablets. Ribavirin and matching placebos were provided as capsules and were identical in appearance. During the treatment period, measures to prevent implicit unblinding by laboratory results were used. Specifically, the results of haemoglobin and haematocrit were blinded to the investigator,

		patient and sponsor until the post-treatment week 12 or premature discontinuation visit, unless criteria for virologic failure or relevant predefined toxicity were met, in which case the relevant laboratory data were unblinded to the investigator, patient, and sponsor.
Intervention(s) (n =) and comparator(s) (n =)	**Group 1 – 3D + RBV** n= 91 **Group 2 – 3D** n= 95	**Intervention: 3D + RBV** n= 210 **Intervention: 3D + placebo** n= 209
Primary outcomes	The primary efficacy end point was non-inferiority of the SVR12 rates (assessed by HCV-RNA level < 25 IU/mL) in group 2 and group 1 to the historical SVR12 rate for telaprevir plus PegIFN/ RBV in HCV genotype 1b–infected patients who were relapsers, partial responders, or null responders to previous PegIFN/RBV treatment, adjusted for non-cirrhotic patients in this study. A fixed-sequence testing procedure was used to control type I error at 0.05. Plasma samples were collected at screening and at each study visit and HCV-RNA levels were determined using the Roche COBAS TaqMan real-time reverse-transcription polymerase chain reaction assay v2.0 at a central laboratory.	The primary efficacy end point was SVR (a plasma HCV RNA level of <25 IU per millilitre) 12 weeks after the end of treatment. The primary objective was to assess the non-inferiority of the rate of SVR at post-treatment week 12 in each study group, as compared with the historical rate with telaprevir plus PegIFN/RBV among previously untreated patients with the corresponding HCV sub-genotype (see statistical analysis below for more details). Plasma HCV RNA levels was determined for each sample collected by the central laboratory using the Roche COBAS TaqMan real-time reverse transcriptase-PCR (RT-PCR) assay v2.0. The lower limit of detection (LLOD) is 15 IU/mL and the LLOQ (lower limit of quantification) is 25 IU/mL.
Secondary outcomes	Secondary efficacy end points in the fixed sequence included the following: • comparison of the percentage of patients with a decrease in haemoglobin level to less than the lower limit of normal at the end of treatment; • superiority of group 1 and group 2 to the historical rate for telaprevir plus PegIFN/RBV (75%); and • non-inferiority of group 2 to group 1 using a 10.5%	Secondary efficacy objectives in each study were to assess: • non-inferiority of the SVR rate in the group that did not receive ribavirin as compared with the group that received ribavirin, • superiority of the rate at post-treatment week 12 in each group as compared with the historical rate with telaprevir plus PegIFN/RBV in the corresponding patient population,

<table>
<tr>
<td></td>
<td>non-inferiority margin for the SVR12 difference.
• The percentage of patients with on-treatment virologic failure and post-treatment relapse also was assessed.</td>
<td>• the percentage of patients in each group with a haemoglobin level below the lower limit of the normal range at the end of treatment, and
• the percentage of patients in each group with virologic failure during treatment or relapse after treatment.</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>For the non-inferiority and superiority analyses, because data were not available by sub-genotype and type of non-response for non-cirrhotic treatment-experienced patients, data from the telaprevir study REALIZE were used with an adjustment factor to account for the exclusion of cirrhotic patients in PEARL-II. For non-cirrhotic genotype 1b-infected patients in PEARL-II, the upper bound of the 95% confidence interval (CI) of SVR rate for telaprevir plus peg/IFN/RBV therapy was 75%, representing a threshold relevant to the overall population enrolled in PEARL-II. For the study regimen to be considered superior to the historical SVR rate for telaprevir, the lower bound of the SVR rate 95% CI must exceed the upper confidence bound of the historical SVR rate for telaprevir based therapy presented in the table below (i.e., 75%).
<table>
<tr><td colspan="5">Estimated SVR Rates for Telaprevir plus pegIFN/RBV Therapy in Treatment-Experienced, Non-cirrhotic Patients with HCV Subgenotype 1b, REALIZE study[1]</td></tr>
<tr><td>Previous non-response</td><td>GT1b T12/PR48 n/N (%)</td><td>With Increase for Excluding Cirrhotics (%)</td><td>Projected Enrollment in PEARL-II (%)</td><td>Population-Based Weighted Average % [95% CI]</td></tr>
<tr><td>Relapsers</td><td>123/140 (87.9)</td><td>88.4</td><td>30</td><td rowspan="3">69 [62, 75]</td></tr>
<tr><td>Partial responders</td><td>27/40 (67.5)</td><td>79.5</td><td>30</td></tr>
<tr><td>Null responders</td><td>22/59 (37.3)</td><td>46.5</td><td>30</td></tr>
<tr><td colspan="5">GT, genotype; T, telaprevir; PR, pegIFN/RBV</td></tr>
</table>
To be considered non-inferior to the historical SVR rate for telaprevir, a non-inferiority margin of 10.5% was used. Thus,</td>
<td>For the non-inferiority and superiority analyses, for genotype 1b-infected patients, the upper bound of the 95% confidence interval (CI) was 84%, representing a threshold relevant to the overall population enrolled in PEARL-III. For the regimen to be considered superior to the historical SVR rate for telaprevir, the lower bound of the 95% CI for the SVR rate was required to exceed the upper confidence bound of the historical SVR rate for telaprevir-based therapy presented in the table below (i.e., 84%). To be considered non-inferior to the historical SVR rate for telaprevir, a non-inferiority margin of 10.5% was used. Thus, non-inferiority to the historical SVR rate for telaprevir based therapy was met if the lower bound of the 95% CI for the SVR rate was greater than the upper confidence bound of the SVR rate for telaprevir-based therapy minus 10.5% (i.e., 73%). The 2-sided 95% confidence intervals were created using the normal approximation to the binomial.
<table>
<tr><td colspan="4">Estimated SVR Rates for Telaprevir plus pegIFN and Ribavirin Therapy in Treatment-naïve Patients with Genotype 1a or 1b</td></tr>
<tr><td>Telaprevir Studies</td><td>ADVANCE T12/PR n/N (%)</td><td>ILLUMINATE T12/PR n/N (%)</td><td>Meta-Analysis % [95% CI]</td></tr>
<tr><td>Treatment-naïve GT1a patients</td><td>162/217 (75)</td><td>273/388 (70)</td><td>72 [68, 75]</td></tr>
<tr><td>Treatment-naïve GT1b patients</td><td>119/142 (84)</td><td>112/149 (75)</td><td>80 [75, 84]</td></tr>
</table>
To test non-inferiority of each study placebo group to its corresponding group with ribavirin, the 2-sided 95% confidence interval for the difference in SVR12 rates (placebo group minus ribavirin group) was calculated using the normal approximation</td>
</tr>
</table>

	non-inferiority to the historical SVR rate for telaprevir based therapy was met if the lower bound of the 95% CI for the regimen SVR rate was greater than the upper confidence bound of SVR rate for the telaprevir based therapy minus 10.5% (i.e., 64%). The 2-sided 95% confidence intervals are created using the normal approximation to the binomial. To test non-inferiority of the RBV-free group compared to the RBV-containing group, the 2-sided 95% confidence interval for the difference in SVR12 rates will be calculated using the normal approximation to the binomial distribution. If the lower bound of the 2-sided 95% confidence interval for the difference was above the non-inferiority margin of -10.5%, non-inferiority can be claimed for the regimen without RBV compared to regimen with RBV. Efficacy analyses were performed using the intent-to-treat population, defined as all randomized HCV genotype 1b–infected patients who received at least one dose of co-formulated ABT-450/ritonavir/ombitasvir. The safety population included all patients who received at least one dose of study drug. SAS software was used for all analyses and all statistical tests and all confidence intervals were 2-sided with a significance level of .05.	to the binomial distribution. If the lower bound of the 2-sided 95% confidence interval for the difference was above the non-inferiority margin of -10.5%, the regimen with placebo was considered non-inferior to the regimen with ribavirin. Efficacy analyses were performed in the modified intention-to-treat population, defined as all randomly assigned patients who received at least one dose of a study drug. Safety analyses compared the rate of adverse events and laboratory abnormalities between treatment groups in each study with the use of Fisher's exact test.
Duration of follow-up	48 week follow-up	48 week follow-up

Table 29: Summary of methodology for PEARL-IV

Trial no. (acronym)	PEARL-IV[35] HCV GT1a – treatment naive
Location	53 sites in Canada, the US and the UK
Design	Phase III, multicentre, randomised, double-blinded, placebo-controlled trial. Patients were stratified according to *IL28B* genotype (CC vs. non-CC) and randomly assigned in a 1:2 ratio to receive either ribavirin twice daily according to body weight (1000 mg daily if the body weight was <75 kg and 1200 mg daily if the body weight was ≥75 kg) or matching placebo for 12 weeks. All the patients received open-label ABT-450/r–ombitasvir (at a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir) and dasabuvir (250 mg twice daily) for 12 weeks:  Visits were scheduled at weeks 0, 1, 2, 4, 6, 8, 10, and 12 of the treatment period, and patients were followed for 48 weeks after the treatment period.
Duration of study	12 week treatment 48 week follow-up
Method of randomisation	At the screening visit, patients were assigned a unique patient number through the use of Interactive Response Technology (IRT). For patients who did not meet the study selection criteria, the site personnel contacted the IRT system and identified the patient as a screen failure. Enrolled patients retained their patient number, assigned at the Screening Visit, throughout the study. For enrolment of eligible patients into the study, the site utilized the IRT system in order to receive unique study drug bottle/kit numbers and a unique randomisation number. The randomisation number was used only by the Sponsor for loading the treatment assignments into the database. The study drug kit numbers and randomisation numbers were assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department. Contact information and user guidelines for IRT use were provided to each site. Upon receipt of study drugs, the site acknowledged

	receipt in the IRT system.
Method of blinding (care provider, patient and outcome assessor)	Treatment assignment was to remain blinded to the investigator, patient, and sponsor. During the Treatment Period, ABT-450/r/ombitasvir and dasabuvir were provided as tablets. Ribavirin and matching placebos were provided as capsules and were identical in appearance. During the treatment period, measures to prevent implicit un-blinding by laboratory results were used. Specifically, the results of haemoglobin and haematocrit were blinded to the investigator, patient and sponsor until the post-treatment week 12 or premature discontinuation visit, unless criteria for virologic failure or relevant predefined toxicity were met, in which case the relevant laboratory data were unblinded to the investigator, patient, and sponsor.
Intervention(s) (n =) and comparator(s) (n =)	**Intervention: 3D + RBV** n= 100 **Intervention: 3D + placebo** n= 205
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy end point was SVR (a plasma HCV RNA level of <25 IU per millilitre) 12 weeks after the end of treatment. The primary objective was to assess the non-inferiority of the rate of SVR at post-treatment week 12 in each study group, as compared with the historical rate with telaprevir plus PegIFN/RBV among previously untreated patients with the corresponding HCV sub-genotype (see statistical analysis below for more details). Plasma HCV RNA levels was determined for each sample collected by the central laboratory using the Roche COBAS TaqMan real-time reverse transcriptase-PCR (RT-PCR) assay v2.0. The lower limit of detection (LLOD) is 15 IU/mL and the LLOQ (lower limit of quantification) is 25 IU/mL.
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy objectives in each study were to assess: • non-inferiority of the SVR rate in the group that did not receive ribavirin as compared with the group that received ribavirin, • superiority of the rate at post-treatment week 12 in each group as compared with the historical rate with telaprevir plus PegIFN/RBV in the corresponding patient population, • the percentage of patients in each group with a haemoglobin level below the lower limit of the normal range at the end of treatment, and • the percentage of patients in each group with virologic failure during treatment or relapse after treatment.
Statistical analysis	For the non-inferiority and superiority analyses for genotype 1a-infected patients, the upper bound of the 95% confidence interval (CI) was 75%, representing a threshold relevant to the overall population enrolled in PEARL-IV. For the regimen to be considered superior to the historical SVR rate for telaprevir, the lower bound of the 95% CI for the SVR rate was required to exceed the upper confidence bound of the historical SVR rate for telaprevir-based therapy presented in the table below

(i.e., 75%). To be considered non-inferior to the historical SVR rate for telaprevir, a non-inferiority margin of 10.5% was used. Thus, non-inferiority to the historical SVR rate for telaprevir based therapy was met if the lower bound of the 95% CI for the SVR rate was greater than the upper confidence bound of the SVR rate for telaprevir-based therapy minus 10.5% (i.e., 65%). The 2-sided 95% confidence intervals were created using the normal approximation to the binomial.

Estimated SVR Rates for Telaprevir plus pegIFN and Ribavirin Therapy in Treatment-naïve Patients with Genotype 1a or 1b

Telaprevir Studies	ADVANCE T12/PR n/N (%)	ILLUMINATE T12/PR n/N (%)	Meta-Analysis % [95% CI]
Treatment-naïve GT1a patients	162/217 (75)	273/388 (70)	72 [68, 75]
Treatment-naïve GT1b patients	119/142 (84)	112/149 (75)	80 [75, 84]

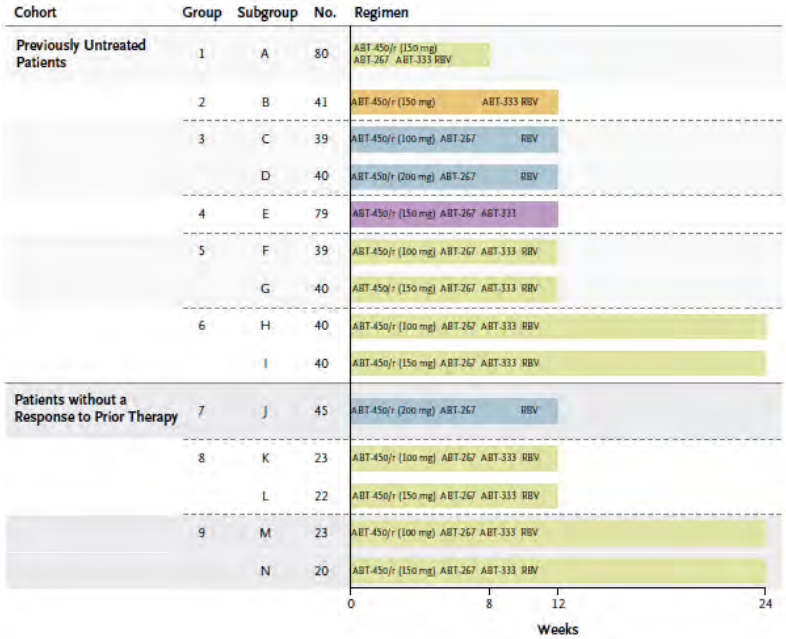
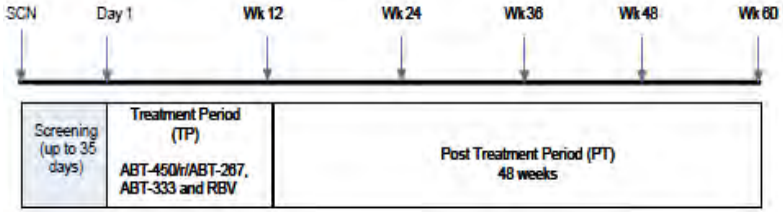
Efficacy analyses were performed in the modified intention-to-treat population, defined as all randomly assigned patients who received at least one dose of a study drug. Safety analyses compared the rate of adverse events and laboratory abnormalities between treatment groups in each study with the use of Fisher's exact test.

Duration of follow-up

48 week follow-up period

Table 30: Summary of methodology for phase II studies - AVIATOR and M14-103

Trial no. (acronym)	AVIATOR HCV GT1 – treatment naïve and treatment experienced	M14-103 HCV GT1 – treatment naïve and treatment experienced on stable opioid replacement therapy
Location	97 sites in the US, Puerto Rico, Canada, France, Germany, Spain, UK, Australia and New Zealand.	8 sites in the USA

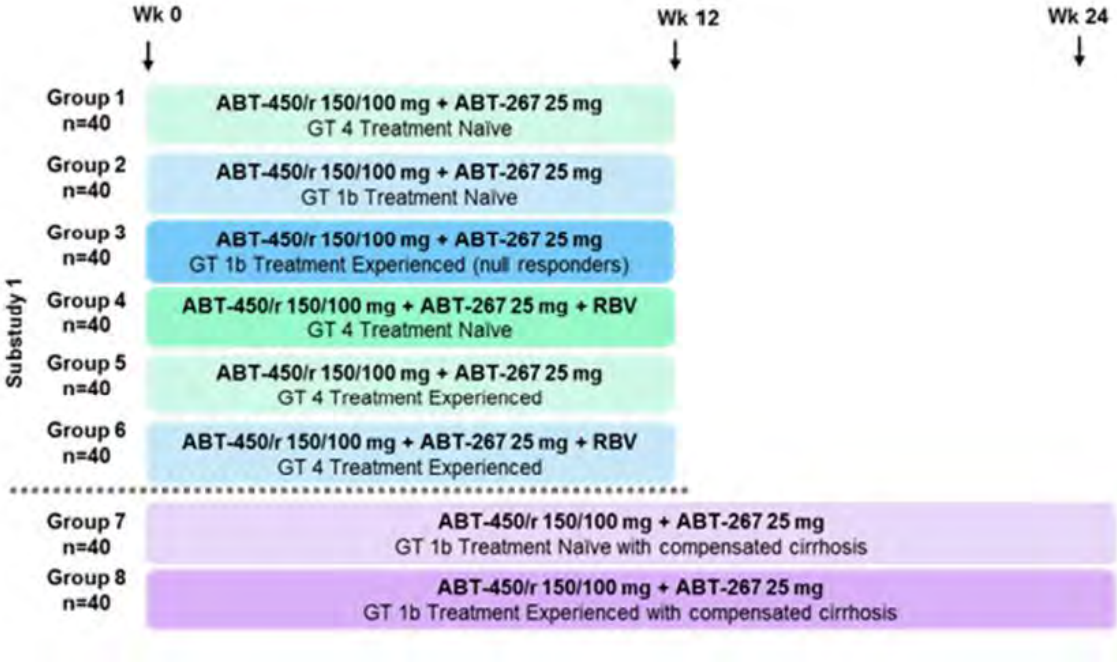
Design	Phase IIb, open-label, multinational, multiple group study. Subjects were stratified by IL28B genotype (CC versus non-CC) and HCV genotype and subtype (1a versus non-1a). Subjects were enrolled in Cohort 1 (Treatment-naïve patients) or Cohort 2 (Prior null responders) according to their previous treatment status.  For treatment-naïve subjects, enrolment into Groups A, F and G was preferential in that subjects were initially randomised in a 2:0:0:0:0:1:1:0:0 ratio to Groups A – I. When a total of 80 subjects were enrolled in this manner (40 subjects are enrolled in Group A and 20 subjects are enrolled in each of Groups F and G), the randomisation continued in a 2:2:2:2:4:1:1:2:2 ratio to Group A – I up to a total of approximately 440 treatment-	Phase II, single-arm, open-label, multicentre study evaluating 3D + RBV in HCV genotype-1 patients without cirrhosis who were either treatment naïve or PegIFN/RBV experienced, and who were on a stable opioid replacement therapy of methadone or buprenorphine ± naloxone. 

	naïve subjects. Null responder subjects were randomised in a 2:1:1:1:1 ratio to Groups J – N up to approximately 120 subjects.	
Duration of study	12 or 24 week treatment period 48 week follow-up	12 week treatment period 48 week follow-up
Method of randomisation	Randomisation was via the Interactive Response Technology (IRT) system. For randomisation of eligible patients, the site contacted the IRT to receive a unique randomization number and study drug kit numbers. The study drug kit numbers were assigned according to a randomisation schedule computer-generated before the start of the study by the sponsor's statistics department.	N/A – single arm
Method of blinding	N/A – open label.	N/A – open label.
Intervention(s) (n =) and comparator(s) (n =)	**Treatment naïve patients – multiple regimens** n=438 **Prior null responders to PegIFN/RBV – multiple regimens** N=133	**Intervention: 3D + RBV** n=38
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint was the comparison of the percentage of treatment-naïve subjects with SVR24 following 8 weeks of treatment with 3D + RBV versus 12 weeks of treatment with 3D + RBV (Group A versus Group G). Logistic regression with treatment group, baseline log10 HCV RNA level, HCV Sub-genotype (1a or non-1a), geographic regions and IL28B genotype (CC, non-CC) as predictors was used to compare the groups. Note SVR was collected 24 weeks post treatment rather than 12 weeks post treatment as it was in all the phase III trials.	The primary efficacy endpoint was the percentage of subjects with SVR12 (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). The simple percentage of subjects with SVR12 was calculated and a 2-sided 95% CI was calculated using the normal approximation of the binomial.

Secondary outcomes (including scoring methods and timings of assessments)	The secondary efficacy endpoints were comparisons of the percentage of subjects with SVR24: • among the subjects treated with 3D + ribavirin for 8 weeks versus 12 weeks (Group A versus Groups[F + G + K + L], • among subjects treated with 3D + ribavirin for 8 versus 24 weeks (Group A versus Groups [H + I + M + N] • among subjects treated with 3D + ribavirin for 12 weeks versus 24 weeks (Groups [F + G + K + L] versus Groups [H + I + M + N]), • among the subjects treated with 2 direct-acting antiviral agents (ABT-450/r + ABT-333)[note not 2D] + ribavirin for 12 weeks versus 3 direct-acting antiviral agents + ribavirin for 12 weeks (Group B versus Groups [F + G + K + L]), • among the subjects treated with 2D + ribavirin for 12 weeks versus 3 direct-acting antiviral agents + ribavirin for 12 weeks (Groups [C + D + J] versus Groups [F + G + K + L]), • among those treated with 3 direct-acting antiviral agents + ribavirin for 12 weeks versus 3 direct-acting antiviral agents without ribavirin for 12 weeks (Groups [F + G+ K + L] versus Group E), and • among treatment-naïve subjects and null responder subjects treated with ABT 450/r + ABT-267 + ABT-333 + ribavirin for 12 or 24 weeks (a combination of Groups F, G, H and I versus a combination of Groups K, L, M, and N). The percentage of subjects with SVR_{24} were compared between the above specified treatment groups using logistic regression with treatment group, baseline log_{10} HCV RNA	The secondary efficacy endpoints were: • the percentage of subjects with on-treatment virologic failure during the Treatment Period (rebound or failure to suppress during treatment [all on-treatment values of HCV RNA ≥ LLOQ] with at least 6 weeks [defined as study drug duration ≥ 36 days] of treatment) and • the percentage of subjects with post-treatment relapse (confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of active study drug [up to and including the SVR12 assessment time point] for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment. Completion of treatment was defined as a study drug duration ≥ 77 days). The simple percentage of subjects with virologic failure and the simple percentage of subjects with post-treatment relapse were calculated, and a corresponding 2-sided 95% CI was calculated using the normal approximation of the binomial.

	level, HCV sub-genotype (1a or non-1a), geographic region, IL28B genotype (CC, non-CC), and ABT-450/r dose and subject populations (treatment-naïve versus null responder, if appropriate) as predictors. The stratum-adjusted Mantel-Haenszel method, controlling for the baseline stratification variables (IL28B genotype [CC and non-CC] and HCV sub-genotype [1a and non-1a]), was also planned for the comparisons of SVR endpoints among the specific groups. It is also presented as the logistic regression analysis encountered separation or quasi-separation among the predictor variables due to the low number of subject failing to achieve SVR.	
Duration of follow-up	SVR assessed 24 weeks post treatment 48 week follow-up post treatment	SVR assessed 12 weeks post treatment 48 week follow-up post treatment

Table 31: Summary of methodology for treatment naïve and PegIFN/RBV experienced HCV-GT4 subjects in PEARL-I [39]

Trial no. (acronym)	PEARL-I HCV GT4 – treatment naïve and treatment experienced
Location	46 sites in the US, Puerto Rico, France, Hungary, Italy, Poland, Romania, Spain and Turkey.
Design	Phase-II, randomised open-label, multinational, combination treatment study. Study arms relevant to the decision problem are Groups 1, 4, 5 and 6. However, based on a protocol-specific interim review of the on-treatment results from the treatment naïve groups 1 and 4 that indicated higher SVR rates among subjects receiving 2D + RBV, only Group 6 was opened for enrolment in treatment-experienced HCV GT4-infected subjects (no subjects were enrolled in group 5).  Treatment-naïve, HCV GT4-infected subjects were randomized in a 1:1 ratio to the 2-DAA regimen for 12 weeks and the 2-DAA regimen plus RBV for 12 weeks (i.e., Groups 1 and 4, respectively). The randomization schedule was stratified by IL28B

	genotype (CC versus non-CC). Group 6 enrolled subjects who are prior null responders, prior partial responders, or prior relapsers to PegIFN/RBV. For each of these groups, the total number of prior partial responders and relapsers was limited to no more than 25 subjects so that at least 15 prior null responders would be enrolled in each group. Treatment-experienced, HCV GT4 subjects were enrolled and assigned to receive 2D + RBV for 12 weeks.
Duration of study	12 week treatment period 48 week follow-up period
Method of randomisation	All subjects were centrally enrolled and assigned to a treatment group using the IRT system. At the Screening Visit, all subjects were assigned a unique subject number through the use of IRT. Unique subject numbers were 5-digit numbers and began with 30001. For subjects who did not meet the study selection criteria, the site personnel contacted the IRT and identified the subject as a screen failure. Enrolment occurred first in Groups 2 and 3, followed by Groups 1 and 4. GT4-infected treatment-naïve subjects were randomised in a 1:1 ratio to Group 1 (2D without RBV) and Group 4 (2D + RBV). Upon review and assessment of available data from this study, enrolment for HCV GT4-infected treatment-experienced subjects was open in Group 6 (2-DAA regimen with RBV treatment), but not Group 5 (2-DAA regimen without RBV treatment), per protocol Amendment 5. If both Groups 5 and 6 had been open for enrolment, HCV GT4-infected treatment-experienced subjects would have been randomised in a 1:1 ratio to Groups 5 and 6.
Method of blinding	Not applicable – this study was open-label.
Intervention(s) (n =) and comparator(s) (n =)	**Group 1: Treatment naïve - 2D** N=44 **Group 4: Treatment naïve – 2D + RBV** N=42 **Group 6: PegIFN/RBV experienced – 2D + RBV** N=49
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint was the percentage of subjects with SVR12 following 12 weeks of treatment (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment group. The primary comparison was between Groups 2 and 3. An additional comparison between Groups 1 and 4 was performed. Virologic response was assessed by HCV RNA in IU/mL at various time points from Study Day 1 through 48 weeks after completion of treatment. As mentioned, the primary pairwise comparison was between the treatment-naïve and prior null responder populations among the HCV GT1b-infected subjects without cirrhosis (Group 2 versus Group 3). The following

	additional comparison was performed: the 12-week 2-DAA regimen with and without RBV were compared among the HCV GT4-infected treatment-naïve subjects (Group 1 versus Group 4).
Secondary outcomes (including scoring methods and timings of assessments)	The secondary efficacy endpoints were: • The percentage of subjects with SVR24 (HCV RNA < LLOQ 24 weeks after the last actual dose of study drug), • The percentage of subjects with on-treatment virologic failure, • The percentage of subjects with post-treatment relapse. For each secondary efficacy variable, comparisons between Groups 1 and 4 and between Groups 2 and 3 were performed.
Statistical analysis	The pairwise comparisons between Groups 1 and 4 and Groups 2 and 3 were performed using a logistic regression model with treatment group, baseline log10 HCV RNA level, and IL28B genotype (CC, non-CC) as predictors. For each treatment group (i.e., Groups 1 – 4, 6 – 8), the number and percentage of subjects with SVR12 were summarized along with exact 95% confidence intervals. In addition, treatment differences (with 95% confidence intervals) for the specified comparisons were estimated using stratum-adjusted Mantel-Haenszel proportion and continuity-corrected variance, adjusting for IL28B genotype (CC or non-CC).
Duration of follow-up	12 week treatment period 48 week follow-up period

Participants

6.3.3 **Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.**

Table 32 describes the inclusion and exclusion criteria applied to each trial. Please note that for trials including treatment experienced HCV patients, definitions of prior response to PegIFN/RBV therapy have been defined as follows:

- Relapsers received at least 36 weeks of PegIFN/RBV and had undetectable HCV RNA at the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up.

- Partial responders received at least 20 weeks of therapy and achieved ≥2 log10 IU/mL reduction in HCV RNA at week 12(weeks 10–16), but failed to achieve HCV RNA undetectable at the end of treatment.

- Null-responders received at least 12 weeks of therapy and failed to achieve a 2 log10 IU/mL reduction in HCV RNA at week 12(weeks 10–16); or received at least 4 weeks of therapy and achieved a <1 log10 IU/mL reduction in HCV RNA at week 4.

Table 32: Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
SAPPHIRE-I[31] (Supplementary appendix)	1. Male or female and age is between 18 and 70 years, inclusive, at time of Screening. 2. Female who is: • practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle) • sexually active with female partners only • postmenopausal for at least 2 years prior to screening (defined as amenorrhoeic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state) • surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s) • of childbearing potential and sexually active with male partner(s): ○ currently using at least one effective method of birth control at the time of screening and agrees to using two effective methods of birth control while receiving study drugs (as outlined in the patient information and consent form or other patient information documents), starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. (Note: Contraceptives containing ethinyl estradiol are not considered effective during study drug treatment.) 3. Sexually active males must be surgically sterile or have male partners only or if with female partner(s) of childbearing potential must agree to practice two effective forms of birth control (as outlined in the patient information and consent form or other patient information documents) throughout the course of the study, starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local	1. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol. 2. Positive test result at screening for Hepatitis B surface antigen (HBsAg) or anti-Human Immunodeficiency virus antibody (HIV Ab). 3. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years. 4. Any current or past clinical evidence of cirrhosis such as ascites or oesophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir score of >3 or Ishak score of > 4. 5. Screening laboratory analyses showing any of the following abnormal laboratory results: • Alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN) • Aspartate aminotransferase (AST) > 5 × ULN • Calculated creatinine clearance (using Cockcroft-Gaultmethod) < 60 mL/min • Albumin < Lower limit of normal (LLN) • Prothrombin time/International normalized ratio (INR) > 1.5. Patients with a known inherited blood disorder and INR > 1.5 may be enrolled with permission of the AbbVie Study Designated Physician • Haemoglobin < LLN • Platelets < 120,000 cells per mm3 • Absolute neutrophil count (ANC) < 1500 cells/μL (< 1200 cells/μL for patients of African descent who are black) · Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN

	ribavirin label. 4. Patient has never received antiviral treatment for hepatitis C infection. 5. Chronic HCV infection is defined as one of the following: • Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or • Positive for anti-HCV Ab and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection. 6. Per local standard practice, documented results of one of the following: • Liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a Metavir Score of 3 or less or an Ishak score of 4 or less; or • a screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or • a screening FibroScan result of < 9.6 kPa. (Patients with a non-qualifying FibroTest/APRI or FibroScan result may only be enrolled if they have a qualifying liver biopsy performed within 24 months prior to or during screening.) 7. Patient has plasma HCV RNA level > 10,000 IU/mL at Screening.	

SAPPHIRE-II[32] (Supplementary appendix)	1. Male or female and age is between 18 and 70 years, inclusive, at time of screening. 2. Patient must have documentation that they were adherent to prior PegIFN/RBV combination therapy and meet one of the following categories: • Null responder: 1. received at least 12 weeks of PegIFN/RBV for the treatment of HCV and failed to achieve a 2 log10 IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16); or 2. received at least 4 weeks of PegIFN/RBV for the treatment of HCV and achieved a < 1 log10 IU/mL reduction in HCV RNA at Week 4 (≥ 25 days); or • Partial responder: received at least 20 weeks of PegIFN/RBV for the treatment of HCV and achieved ≥ 2 log10 IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or • Relapser: received at least 36 weeks of PegIFN/RBV for the treatment of HCV and was undetectable at or after the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up Viral loads documenting the type of prior non-response should be obtained during the previous PegIFN/RBV treatment. PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit. 3. Chronic HCV infection is defined as one of the following: • Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or • Positive for anti-HCV Ab and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrolment with evidence of chronic hepatitis C disease). 4. Screening laboratory result indicating HCV genotype 1-infection.	1. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol. 2. Positive test result for Hepatitis B surface antigen (HBsAg) or anti-Human Immunodeficiency virus antibody (HIV Ab). 3. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated haemoglobin (haemoglobin A1C) level > 8.5%, at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years. 4. Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir Score of >3 or Ishak score of > 4. 5. Screening laboratory analyses showing any of the following abnormal laboratory results: • Alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN) • Aspartate aminotransferase (AST) > 5 × ULN • Calculated creatinine clearance (using Cockcroft-Gaultmethod) < 60 mL/min • Albumin < Lower limit of normal (LLN) • Prothrombin time/International normalized ratio (INR) > 1.5. Patients with a known inherited blood disorder may be enrolled with permission of the AbbVie Study Designated Physician even if the INR > 1.5 • Haemoglobin < LLN • Platelets < 120,000 cells per mm3 • Absolute neutrophil count (ANC) < 1500 cells/μL (< 1200 cells/μL for patients of African descent who are black) • Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN

	5. Per local standard practice, documented results of one of the following: • A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a METAVIR Score of 3 or less, Ishak score of 4 or less; or • A screening FibroTest® score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or • A screening FibroScan® result of < 9.6 kPa. Patients with a non-qualifying Fibrotest®/APRI or Fibroscan result may only be enrolled if they have a qualifying liver biopsy performed within 24 months prior to or during screening. 6. Patient has plasma HCV RNA level > 10,000 IU/mL at Screening.	

TURQUOISE-II [33] (Supplementary appendix)	1. Male or female and age is between 18 and 70 years, inclusive, at time of Screening. 2. Female who is: • practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle) • sexually active with female partners only • postmenopausal for at least 2 years prior to screening (defined as amenorrhoeic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state) • surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s) • of childbearing potential and sexually active with male partner(s): ○ currently using at least one effective method of birth control at the time of screening and agrees to using two effective methods of birth control while receiving study drugs (as outlined in the patient information and consent form or other patient information documents), starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. (Note: Contraceptives containing ethinyl estradiol are not considered effective during study drug treatment.) 3. Sexually active males must be surgically sterile or have male partners only or if with female partner(s) of childbearing potential must agree to practice two effective forms of birth control (as outlined in the patient information and consent form or other patient information documents) throughout the course of the study, starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. 4. Patient has never received antiviral treatment (including	1. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol. 2. Positive test result at Screening for hepatitis B surface antigen or anti-human immunodeficiency virus antibody. 3. HCV genotype performed during screening indicating unable to genotype or co-infection with any other HCV genotype. 4. Prior therapy with DAAs for the treatment of HCV, including telaprevir and boceprevir. 5. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated haemoglobin (haemoglobin A1C) level > 8.5% at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years. 6. Any current or past clinical evidence of Child-Pugh B or C Classification or clinical history of liver decompensation including ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy. 7. Serum Alpha-Fetoprotein > 100 ng/mL at Screening. 8. A positive screening ultrasound for hepatocellular carcinoma confirmed with a subsequent CT scan or MRI during the screening period. 9. Any cause of liver disease other than chronic HCV-infection, including but not limited to the following: • Hemochromatosis • Alpha-1 antitrypsin deficiency • Wilson's disease • Autoimmune hepatitis • Alcoholic liver disease • Drug-related liver disease ○ Steatosis and steatohepatitis on a liver biopsy coincident with HCV-related changes would not be considered exclusionary unless the steatohepatitis is considered to be the primary cause of the liver disease.

	pegIFN/RBV) for hepatitis C infection (treatment-naïve patient), or patient must have documentation that they were adherent to prior pegIFN/RBV therapy and meet one of the following categories (treatment-experienced patient):
	• Null-responder:
	  ○ received at least 12 weeks of PegIFN/RBV for the treatment of HCV and failed to achieve a 2 log10 IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16); or
	  ○ received at least 4 weeks of PegIFN/RBV for the treatment of HCV and achieved a < 1 log10 IU/mL reduction in HCV RNA at Week 4 (≥ 25 days); or
	• Partial responder: received at least 20 weeks of PegIFN/RBV for the treatment of HCV and achieved ≥ 2 log10 reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or
	• Relapser: received at least 36 weeks of PegIFN/RBV for the treatment of HCV and was undetectable at or after the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up.
	  ○ HCV RNA levels that serve as documentation to support the type of prior non-response should have been obtained in relation to the previous PegIFN/RBV treatment. PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit.
	5. Chronic HCV infection is defined as one of the following:
	• Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
	• Positive for anti-HCV Ab and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrolment with evidence of chronic hepatitis C disease).
		10. Screening laboratory analyses showing any of the following abnormal laboratory results:
		• Alanine aminotransferase (ALT) > 7 × upper limit of normal (ULN)
		• Aspartate aminotransferase (AST) > 7 × ULN
		• Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
		• Albumin < 2.8 g/dL
		• International normalized ratio (INR) > 2.3. Patients with a known inherited blood disorder and INR > 2.3 may be enrolled with permission of the AbbVie Study Designated Physician
		• Haemoglobin < LLN
		• Platelets < 60,000 cells per mm3
		• Absolute neutrophil count < 1500 cells/μL (< 1200 cells/μL for patients of black race or patients of African descent who are black)
		• Total bilirubin ≥ 3.0 mg/dL

	6. Screening laboratory result indicating HCV genotype 1-infection. 7. Per local standard practice, documentation of cirrhosis by one of the following methods: • Previous histologic diagnosis on liver biopsy, e.g., Metavir Score of > 3 (including 3/4 or 3–4), Ishak score of > 4 or, • FibroScan score ≥ 14.6 kPa within 6 months of Screening or during the Screening Period. (Patients with a non-qualifying FibroScan result may only be enrolled if they have a qualifying liver biopsy performed during screening.) 8. Compensated cirrhosis defined as Child-Pugh score of <7 at Screening. 9. Patient has plasma HCV RNA level > 10,000 IU/mL at Screening. 10. Absence of hepatocellular carcinoma as indicated by negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) performed within 3 months prior to Screening or a negative ultrasound at Screening.	

PEARL-II[34] (Andreone et al Supplementary appendix)	1. Male or female between 18 and 70 years of age, inclusive, at time of Screening. 2. Female who is: • practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle) • sexually active with female partners only • not of childbearing potential, defined as: ○ postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state), or ○ surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s). • of childbearing potential and sexually active with male partner(s): • of childbearing potential and sexually active with male partner(s) currently using at least one effective method of birth control at the time of screening and two effective methods of birth control while receiving study drugs, starting with Study Day 1 and for 7 months after stopping study drug as directed by the local ribavirin label. (Note: Hormonal contraceptives, including oral, topical, injectable or implantable varieties, may not be used during study drug treatment.) 3. Females must have had negative results for pregnancy tests performed: at screening by serum specimen within 35 days prior to initial study drug administration; and at baseline (prior to dosing) by urine specimen. 4. Sexually active males must have been surgically sterile or	1. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol. 2. Positive test result for Hepatitis B surface antigen (HBsAg) or anti-Human immunodeficiency virus antibody (HIV Ab). 3. Patient's HCV sub-genotype at screening was not sub-genotype 1b or indicated co-infection of 1b with any other genotype/sub-genotype. 4. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated haemoglobin (haemoglobin A1C) level > 8.5% at the Screening visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years. 5. Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir score of >3 or Ishak score of > 4. 6. Any cause of liver disease other than chronic HCV infection, including but not limited to the following: • hemochromatosis; • alpha-1 antitrypsin deficiency; • Wilson's disease; • autoimmune hepatitis; • alcoholic liver disease; Steatosis and steatohepatitis on a liver biopsy coincident with HCV-related changes would not have been considered exclusionary unless the steatohepatitis was considered to be the primary cause of liver disease.

	have had male partners only or if sexually active with female partner(s) of childbearing potential must have agreed to practice 2 effective forms of birth throughout the course of the study, starting with Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin (RBV) label. (Note: Contraceptives containing ethinyl estradiol or depo progesterone were considered effective if used by the female partners of male patients.) 5. Patient must have had documentation that they were adherent to prior PegIFN/RBV combination therapy and met 1 of the following categories: • Null responders: received at least 12 weeks of PegIFN/RBV for the treatment of HCV and failed to achieve a 2 log10 IU/mL reduction in HCV RNA at Week 12. Patients were considered to have met this definition if the lack of treatment response was documented following 10 to 16 weeks of treatment; • Non-responders/partial responders: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved ≥ 2 log10 IU/mL reduction in HCV RNA at Week 12, but failed to achieve HCV RNA undetectable at the end of treatment. Patients were considered to have met this definition if the lack of treatment response was documented following 10 to 16 weeks of treatment; or • Relapsers: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up. Viral loads documenting the type of prior nonresponse were to be obtained during the previous PegIFN/RBV treatment. PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit. 6. Chronic HCV genotype 1b-infection for at least 6 months prior	7. Screening laboratory analyses showing any of the following abnormal laboratory results: • Alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN) • Aspartate aminotransferase (AST) > 5 × ULN • Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min • Albumin < Lower limit of normal (LLN) • Prothrombin time/International normalized ratio (INR) > 1.5. Patients with a known inherited blood disorder and INR > 1.5 may be enrolled with permission of the AbbVie Study Designated Physician, even if the INR > 1.5 • Haemoglobin < LLN • Platelets < 120,000 cells per mm3 • Absolute neutrophil count (ANC) < 1500 cells/μL (< 1200 cells/μL for patients of African descent who are black) • Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN 8. Use of any medications listed below, as well as those that are contraindicated for ritonavir and ribavirin, within 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer, including but not limited to: • Alfuzosin • Amiodarone

	to Screening. Chronic HCV infection is defined as one of the following: • positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before screening, and positive for HCV RNA and anti-HCV Ab at the time of screening or • positive for anti-HCV Ab and HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection. 7. Per local standard practice, documented results of 1 of the following: • liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a Metavir score of 3 or less or an Ishak score of 4 or less; • screening FibroTest score of ≤ 0.72 and aspartate aminotransferase (AST) to platelet ratio index (APRI) ≤ 2; or • screening FibroScan® result of < 9.6 kPa; Patients with a nonqualifying FibroTest/APRI or FibroScan could have only been enrolled if they had a qualifying liver biopsy within 24 months prior to or during screening. 8. Patient had plasma HCV RNA level > 10,000 international units (IU)/mL at screening. 9. Patient's HCV genotype was sub-genotype 1b at screening without co-infection with any other genotype/sub-genotype.	• Astemizole • Bepridil • Bosentan • Buprenorphine • Carbamazepine • Cisapride • Clarithromycin • Conivaptan • Lovastatin • Methadone • Midazolam (oral) • Mifepristone • Modafinil • Montelukast • Nefazodone • Phenobarbital • Phenytoin • Pimozide • Pioglitazone • Propafenone • Quercetin • Quinidine • Rifabutin • Rifampin • Rosiglitazone • Salmeterol • Simvastatin • St. John's Wort • Telithromycin • Terfenadine • Triazolam • Trimethoprim • Troglitazone • Troleandomycin

		• Voriconazole

PEARL-III and PEARL-IV[35] (Ferenci et al Supplementary appendix)	1. Male or female between 18 and 70 years of age, inclusive, at time of Screening. 2. Female who is: • Not of childbearing potential, defined as: ○ postmenopausal for at least 2 years prior to screening (defined as amenorrheic forlonger than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state), or ○ surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or has a vasectomized partner, or o practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle), or ○ sexually active with female partners only. • of childbearing potential and sexually active with male partner(s) currently using at least one effective method of birth control at the time of screening and two effective methods of birth control while receiving study drugs, starting with Study Day 1 and for 7 months after stopping study drug as directed by the local ribavirin label. (Note: Hormonal contraceptives, including oral, topical, injectable or implantable varieties, may not be used during administration of study drugs). 3. Sexually active males must be surgically sterile or have male partners only or if sexually active with female partner(s) of childbearing potential must agree to practice two effective forms of birth throughout the course of the study, starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. 4. Patient has never received antiviral treatment for hepatitis C infection. 5. Body Mass Index (BMI) is from ≥ 18 to < 38 kg/m2 at the time of Screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in	1. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol. 2. Positive test result for Hepatitis B surface antigen (HBsAg) or anti-Human immunodeficiency virus antibody (HIV Ab). 3. HCV genotype performed during screening indicates more than 1 subtype or co-infection with any other genotype. 4. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated haemoglobin (haemoglobin A1C) level > 8.5% at the Screening visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years. 5. Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir score of >3 or Ishak score of > 4. 6. Screening laboratory analyses showing any of the following abnormal laboratory results: • Alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN) • Aspartate aminotransferase (AST) > 5 × ULN • Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min • Albumin < Lower limit of normal (LLN) • Prothrombin time/International normalized ratio (INR) > 1.5. Patients with a known inherited blood disorder and INR > 1.5 may be enrolled with permission of the AbbVie Study Designated Physician • Haemoglobin < LLN • Platelets < 120,000 cells per mm3 • Absolute neutrophil count (ANC) < 1500 cells/μL (< 1200 cells/μL for patients of African descent who are black) • Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN

	meters (m). 6. Chronic HCV infection as defined by one of the following: • Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or • Positive for anti-HCV Ab and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrolment with evidence of chronic hepatitis C disease). 7. Screening laboratory result indicating HCV genotype 1a infection for PEARL-IV, or genotype 1b infection for PEARL-III. 8. Per local standard practice, documented results of one of the following: • Liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a Metavir score of 3 or less or an Ishak score of 4 or less; or • Screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or • Screening FibroScan® result of < 9.6 kPa; (Patients with a non-qualifying FibroTest/APRI or FibroScan may only be enrolled if they have a qualifying liver biopsy within 24 months prior to or during screening.) 9. Patient has plasma HCV RNA level > 10,000 IU/mL at Screening.	

AVIATOR[36] (Kowdley et al supplementary appendix)	1. Male or female between the age of 18 and 70 years, inclusive, at time of randomisation. 2. If female, subject is either: • postmenopausal for at least 2 years (defined as amenorrhoeic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone (FSH) level indicating a postmenopausal state), or • surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or of childbearing potential subject and is currently practicing one of the following methods of birth control: o total abstinence from sexual intercourse (minimum one complete menstrual cycle); o vasectomized partner(s); o intrauterine device (IUD); or o double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams). 3. Female subjects of childbearing potential must be willing to use two effective forms of birth control (not including oral contraceptives or contraceptives containing ethinyl estradiol) throughout the study and for 6 months (or per local regulations) after stopping study drugs. 4. Females must have negative results for pregnancy tests performed: • At Screening on a serum specimen obtained within 35 days prior to initial study drug administration, and • On a urine sample obtained on Study Day 1 (prior to dosing). 5. Males must be surgically sterile or agree to practicing two effective forms of birth control as follows throughout the course of the study, starting with Study Day 1 and for 6 months after the last dose of study drugs: • Abstinence, • Partner(s) using an intrauterine device (IUD),	1. History of severe, life-threatening or other significant sensitivity to any drug. 2. Use of any herbal supplements (including milk thistle) within the 2-week period prior to the first dose of study drug. 3. Females who are pregnant or breastfeeding or males whose partner is pregnant. 4. Recent (within 6-months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol. 5. Positive test result for hepatitis B surface antigen (HBsAg) or anti-HIV antibodies (anti-HIV Ab). 6. Use of any medications that are contraindicated for use with either ritonavir or ribavirin within 2 weeks prior to study drug administration or 10 half-lives whichever is longer. • Amiodarone • Bepridil • Flecainide • Propafenone • Quinidine • Ergot derivatives (e.g., dihydroergotamine, ergonovine) • Oral midazolam or triazolam • Pimozide • Lovastatin, simvastatin • Cisapride • Alfuzosin HCl Refer to the most current package inserts for a complete list of contraindicated medications. 7. Use of known inhibitors (e.g., ketoconazole) or inducers (e.g., phenobarbital, rifampin, carbamazepine, St. John's Wort) of cytochrome P450 3A (CYP3A), cytochrome P450 2C8 (CYP2C8) (e.g., gemfibrozil, montelukast) and organic anion transporting polypeptide 1B1 (OATP1B1), (e.g., cyclosporine) within 1 month prior to study drug administration. 8. Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, and propoxyphene with the

	• Partner(s) using oral, injected, or implanted methods of hormonal contraceptives, • Subject and/or partner(s) using double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams). 6. Subject must meet one of the following: • Treatment-naïve: Subject has never received antiviral treatment for hepatitis C infection, OR • Prior null responders: Subject has documentation that they previously received PegIFN/RBV for at least 12 weeks and failed to achieve a 2 log10 HCV RNA decrease at Week 12. Subjects may be considered to meet this definition if the lack of treatment response was documented up to 2 weeks prior to treatment Week 12 with the approval of the Study Designated Physician. 7. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements. 8. Body mass index (BMI) is > 18 to < 38 kg/m2. Body mass index is calculated as weight measured in kg divided by the square of height measured in meters (m). 9. Must voluntarily sign and date an informed consent, approved by an Institutional Review Board/Ethics Committee (IRB/EC), prior to the initiation of any screening or study-specific procedures. 10. Chronic HCV genotype 1-infection for at least 6 months prior to study enrollment. Chronic HCV infection is defined as one of the following: • Positive for anti-HCV antibody or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV antibody at the time of Screening; or • Positive for anti-HCV antibody and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrolment with evidence of chronic hepatitis C disease). 11. Per local standard practice, documented results of:	exception of a positive result (including methadone), associated with documented short-term use or chronic stable use of a prescribed medication in that class. 9. Clinically significant abnormalities, other than HCV infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the Investigator. 10. History of uncontrolled seizures, cancer (except basal cell carcinoma of the skin), or uncontrolled diabetes, as defined by a haemoglobin A1C level > 8.0%. 11. Any current or past clinical evidence of cirrhosis (e.g., ascites, oesophageal varices), or a liver biopsy showing cirrhosis. 12. Any cause of liver disease other than chronic HCV infection, including but not limited to the following: • Hemochromatosis • Alpha-1 antitrypsin deficiency • Wilson's disease • Autoimmune hepatitis • Alcoholic liver disease • Nonalcoholic steatohepatitis • Drug-related liver disease 13. Screening laboratory analyses show any of the following abnormal laboratory results: • Alanine aminotransferase (ALT) > 5 X upper limit of normal (ULN), • Aspartate aminotransferase (AST) > 5 X ULN, • Calculated creatinine clearance (using Cockcroft-Gault method) < 50 mL/min, • Albumin < lower limit of normal (LLN), • Prothrombin time INR > 1.5, • Haemoglobin < LLN, • Platelets < 120,000 cells per mm3 for subjects with METAVIR score < 3 or Ishak score < 4 on a biopsy within the last 3 years; f for subjects with METAVIR score of 3 or Ishak score of 4, platelets < LLN,

	• Fibro Test score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2 at Screening, or • FibroScan® result of < 9.6 kPa, or • the absence of cirrhosis based on a liver biopsy within the last 36 months. 12. Subject has a plasma HCV RNA level > 50,000 International Units (IU)/mL at Screening.	• Absolute neutrophil count < 1500 cells/μL, • Total bilirubin > 1.5 mg/dL, • HCV RNA levels that are above the level of assay quantification. 14. Clinically significant abnormal ECG or ECG with QTc using Fridericia's correction formula (QTcF) > 450 msec at Screening or Day 1 (prior to dosing). 15. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks prior to study drug administration. 16. Consideration by the Investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-450, ABT-267, ABT-333, ritonavir, or ribavirin. 17. Current enrolment in another clinical study or previous use of any investigational or commercially available anti-HCV agents including previous exposure to ABT-450, ABT-267, ABT-333, ritonavir. 18. The use of colony stimulating factors, such as granulocyte colony stimulating factor (GCSF) or erythropoietin within 2 months of the Screening Period. If there were multiple assessments on the same date for a subject, fibrosis score was calculated in the order of liver biopsy, FibroScan, and Fibro Test. If there were assessments on different dates for a subject by different methods, fibrosis score was calculated in the order of liver biopsy, FibroScan, and Fibro Test. If there were assessments on different dates for a subject by the same method, fibrosis score was calculated by maximum value.

<table>
<tr>
<td>M14-103
(CSR)</td>
<td>1. Male or female and age between 18 and 70 years, inclusive, at the time of enrolment.
2. Female who was:
• of childbearing potential and sexually active with male partner(s):
o currently using at least 1 effective method of birth control at the time of screening and agreed to practice 2 effective methods of birth control while receiving study drugs, starting with Day 1 and for 7 months after stopping study drug, as directed by the local RBV label. Hormonal contraceptives, including oral, topical, injectable, or implantable varieties, were not to be used during study drug treatment.
• not of childbearing potential, defined as:
o postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state); or
o surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or had a vasectomized partner(s);
o practiced total abstinence from sexual intercourse (minimum 1 complete menstrual cycle);
o sexually active with female partners only.
3. Females must have had negative results (unless otherwise noted below) for pregnancy tests performed:
• at screening by serum specimen within 35 days prior to initial study drug administration; and
• at baseline (prior to dosing) by urine specimen.
4. Female subjects with a borderline hCG result at screening and/or Day 1 may have enrolled into the study if they either:
• had a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy; or
• were confirmed to be postmenopausal, defined as</td>
<td>1. History of severe, life-threatening sensitivity to any drug.
2. Use of any herbal supplements (including milk thistle) within 2 weeks prior to the first dose of study drug.
3. Females who were pregnant or planned to become pregnant, or breastfeeding, or males whose partners were pregnant or planning to become pregnant within 7 months (or per local RBV label) after their last dose of study drug.
4. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could have precluded adherence to the protocol.
5. Positive test result at screening for hepatitis B surface antigen (HBsAg) or anti-HIV Ab.
6. HCV genotype performed during screening indicated co-infection with any genotype other than genotype 1.
7. Use of any medications listed in the table below within 2 weeks prior to study drug administration, including but not limited to:
<table>
<tr><td>Alfuzosin</td><td>Gemfibrozil</td><td>Rifabutin</td></tr>
<tr><td>Amiodarone</td><td>Itraconazole</td><td>Rifampin</td></tr>
<tr><td>Astemizole</td><td>Ketoconazole (oral)</td><td>Rosiglitazone</td></tr>
<tr><td>Bepridil</td><td>Lovastatin</td><td>Rivaroxaban</td></tr>
<tr><td>Bosentan</td><td>Midazolam (oral)</td><td>Salmeterol</td></tr>
<tr><td>Carbamazepine</td><td>Mifepristone</td><td>Simvastatin</td></tr>
<tr><td>Cisapride</td><td>Modafinil</td><td>St. John's Wort</td></tr>
<tr><td>Clarithromycin</td><td>Montelukast</td><td>Telithromycin</td></tr>
<tr><td>Conivaptan</td><td>Nefazodone</td><td>Terfenadine</td></tr>
<tr><td>Dronedarone</td><td>Phenobarbital</td><td>Triazolam</td></tr>
<tr><td>Efavirenz</td><td>Phenytoin</td><td>Trimethoprim</td></tr>
<tr><td>Eleptriptan</td><td>Pimozide</td><td>Troglitazone</td></tr>
<tr><td>Eplerenone</td><td>Pioglitazone</td><td>Troleandomycin</td></tr>
<tr><td>Ergot derivatives</td><td>Propafenone</td><td>Voriconazole</td></tr>
<tr><td>Everolimus</td><td>Quercetin</td><td>Hormonal contraceptives[a]</td></tr>
<tr><td>Fusidic Acid</td><td>Quinidine</td><td></td></tr>
</table>
8. Use of known strong inhibitors or inducers of cytochrome P450 3A (CYP3A), inhibitors of cytochrome P450 2C8 (CYP2C8) within 2 weeks of the respective medication/supplement, prior to study drug administration.
9. Positive result of a urine drug screen at the Screening Visit for barbiturates, amphetamines, cocaine, benzodiazepines,</td>
</tr>
</table>

	amenorrheic for longer than 2 years, age appropriate, and confirmed by a FSH level indicating a postmenopausal state at screening. 5. Sexually active males must have been surgically sterile or had male partners only, or if sexually active with female partner(s) of childbearing potential, must have agreed to practice effective forms of birth control throughout the course of the study, starting with Day 1 and for 7 months after stopping study drug or as directed by the local RBV label. Contraceptives containing ethinyl estradiol or depo-progesterone would have been considered effective if used by the female partners of male subjects. 6. Subjects must have been HCV treatment-naïve or previous PegIFN/RBV treatment-experienced. If treatment-experienced, subject must have had documentation that they had adhered to prior PegIFN/RBV combination therapy and met 1 of the following categories: • Null responder: o received at least 12 weeks of PegIFN/RBV for the treatment of HCV and failed to achieve a 2 log10 IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16); o received at least 4 weeks of pegIFN/RBV for the treatment of HCV and achieved a < 1 log10 IU/mL reduction in HCV RNA at Week 4 (≥ 25 days); or • Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved ≥ 2 log10 IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or • Relapser: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and HCV RNA was undetectable at or after the end of treatment, but was detectable within 52 weeks of treatment follow-up. Viral loads documenting the type of prior nonresponse were to be obtained in relation to the previous PegIFN/RBV treatment.	phencyclidine, propoxyphene, or alcohol, with the exception of: • a positive result associated with a documented stable opioid replacement therapy of methadone or buprenorphine ± naloxone; • a positive result associated with documented short-term use or chronic stable use of a prescribed medication in that class; • a single positive result on urine screen for alcohol. 10. Clinically significant abnormalities, other than HCV infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram (ECG) that made the subject an unsuitable candidate for this study, in the opinion of the investigator. 11. History of uncontrolled seizures or uncontrolled diabetes, as defined by a haemoglobin A1C (HbA1c, glycated haemoglobin) level > 8.5% at the Screening Visit, active or suspected malignancy, or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years. 12. Any current or past clinical evidence of cirrhosis, such as ascites or oesophageal varices, or prior biopsy showing cirrhosis (e.g., a Metavir score > 3 or an Ishak score > 4). 13. Any cause of liver disease other than chronic HCV infection, including but not limited to: • hemochromatosis • alpha-1 antitrypsin deficiency • Wilson's disease • autoimmune hepatitis • alcoholic liver disease • drug-related liver disease Steatosis and steatohepatitis on a liver biopsy coincident with HCV-related changes were not to be considered exclusionary unless the steatohepatitis was considered to be the primary cause of the liver disease.

	PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit. 7. Subjects must have been on a stable opioid replacement therapy of methadone or buprenorphine ± naloxone for at least 6 months prior to screening. 8. Subjects must have been able to understand and adhere to the study visit schedule and all other protocol requirements. 9. Body mass index (BMI) was from ≥ 18 to < 38 kg/m2 at the time of screening. BMI was calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m). 10. Must have voluntarily signed and dated an ICF, approved by an IRB/IEC, prior to the initiation of any screening or study-specific procedures. 11. Chronic HCV infection prior to study enrolment. Chronic HCV infection was defined as 1 of the following: • Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before screening, and positive for HCV RNA and anti-HCV Ab at the time of screening; or • Positive for anti-HCV Ab and HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrolment with evidence of chronic hepatitis C disease). 12. Screening laboratory result indicating HCV genotype 1-infection. 13. Absence of cirrhosis, as documented by results of 1 of the following: • A liver biopsy within 24 months prior to or during screening, demonstrating the absence of cirrhosis (e.g., a METAVIR Score of 3 or less, Ishak score of 4 or less); or • A screening FibroTest score of ≤ 0.72 and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) ≤ 2; or • Subjects with a nonqualifying Fibrotest/APRI result would have been allowed to enrol only if they had a qualifying	14. Screening laboratory analyses showing any of the following abnormal laboratory results: • alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN); • AST > 5 × ULN; • calculated creatinine clearance (CrCl) (using Cockcroft-Gault method) < 60 mL/min; • albumin < lower limit of normal (LLN); prothrombin time/international normalized ratio (INR) > 1.5. Subjects with a known inherited blood disorder and INR > 1.5 may have been enrolled with permission of the AbbVie study-designated physician; • haemoglobin < LLN; • platelets < 120,000 cells per mm3; • absolute neutrophil count < 1,500 cells/µL (< 1,200 cells/µL for subjects of African descent who were black); • Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN. 15. Clinically significant abnormal ECG, or ECG with QT interval corrected for heart rate using Fridericia's correction formula > 470 msec at screening or Day 1 (prior to dosing). 16. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks prior to study drug administration. 17. Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive ABT-450, ABT-267, ABT-333, ritonavir, or RBV. 18. Current enrolment in another clinical study, previous enrolment in this study, or previous use of any investigational or commercially available anti-HCV therapy (other than interferon and/or PegIFN/RBV), including previous exposure to telaprevir, boceprevir, ABT-450, ABT-267, or ABT-333. Subjects who previously participated in trials of investigational anti-HCV agents may have been enrolled with the approval of the AbbVie study-designated physician if they produced documentation that they received only placebo. Concurrent

	liver biopsy performed within 24 months prior to or during screening. 14. Subject had a plasma HCV RNA level > 10,000 IU/mL at screening.	participation in a non-interventional, epidemiologic, or registry trial might have been permitted with approval by the AbbVie study-designated physician. 19. The use of colony stimulating factors, such as granulocyte colony stimulating factor or erythropoietin within 2 months of the Screening Period. 20. Uncontrolled clinically significant cardiac, respiratory (except mild asthma), hepatic (except HCV-related disease), gastrointestinal, hematologic, or psychiatric disease or disorder, or any uncontrolled medical illness, which was unrelated to the hepatic disease.

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
PEARL-I (CSR)[39]	1. Male or female between 18 and 70 years, inclusive, at time of enrolment. 2. Female who was: • practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle) • sexually active with female partners only • not of childbearing potential, defined as: ○ postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state), or ○ surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s); • of childbearing potential and sexually active with male partner(s): ○ currently using at least one effective method of birth control at the time of screening and two effective methods of birth control while receiving study drugs, starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local RBV label (Group 4 and Group 6 only), as applicable (Note: Hormonal contraceptives, including oral, topical, injectable or implantable [hormone eluting intrauterine devices [IUDs] varieties, were not allowed during study drug treatment). 3. Females were required to have negative results for pregnancy tests performed: • at Screening on a serum specimen obtained within 35 days prior to initial study drug administration, and • on a urine specimen obtained on Study Day 1 (prior to	1. History of severe, life-threatening or other significant sensitivity to any drug. 2. Use of any herbal supplements (including milk thistle) within the 2-week period prior to the first dose of study drug. 3. Females who were pregnant or planned to become pregnant, or breastfeeding, or GT4-infected males whose partners were pregnant or planning to become pregnant within 7 months (or per local RBV label) after their last dose of study drug/RBV. 4. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that, in the opinion of the investigator, could have precluded adherence to the protocol. 5. Positive test result for hepatitis B surface antigen (HBsAg) or anti-HIV Ab. 6. Use of any medications listed below, as well as those that are contraindicated for ritonavir and RBV, within 2 weeks prior to study drug administration or 10 half-lives, whichever was longer, including but not limited to: Alfuzosin, Amiodarone, Astemizole Bepridil, Bosentan, Buprenorphine Clarithromycin, Carbamazepine, Cisapride Conivaptan, Dronedarone, Efavirenz Eleptriptan, Eplerenone, Ergot derivatives Everolimus, Fusidic acid, Itraconazole Ketoconazole, Lovastatin, Methadone Midazolam (oral), Mifepristone, Modafinil Nefazodone, Phenobarbital, Phenytoin Pimozide, Propafenone, Quinidine Rifabutin, Rifampin, Salmeterol Simvastatin, St. John's Wort, Telithromycin Terfenadine, Triazolam, Trimethoprim Troglitazone, Troleandomycin, Voriconazole Hormonal contraceptives [a] a. Use of hormonal contraceptives required approval from the

	dosing). 4. Sexually active males had to be surgically sterile or have male partners only or if sexually active with female partner(s) of childbearing potential had to agree to practice two effective forms of birth control throughout the course of the study, starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local RBV label (Group 4 and Group 6 only), as applicable. 5. Subject had to meet one of the following: • Treatment-naïve: Subject had never received antiviral treatment for HCV infection (Subjects with HCV GT1b infection with or without cirrhosis or HCV GT4 infection; Groups 1, 2, 4, and 7); *OR* • Prior null responders: Subject had documentation that they previously received PegIFN/RBV for at least 10 weeks and failed to achieve a 2 log10 IU/mL HCV RNA decrease at Week 12 (Weeks 10 – 16) (Subjects with HCV GT1b infection with or without compensated cirrhosis or HCV GT4 infection; Groups 3, 5, 6, and 8); *OR* • Partial responder: Subject received at least 20 weeks of PegIFN/RBV for the treatment of HCV and achieved ≥ 2 log10 reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment (Subjects with HCV GT1b infection and compensated cirrhosis or HCV GT4 infection; Groups 5, 6, and 8); *OR* • Relapser: Subject received at least 36 weeks of PegIFN/RBV for the treatment of HCV and was undetectable at the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up (Subjects with HCV GT1b infection and compensated cirrhosis or HCV GT4 infection; Groups 5, 6, and 8).	AbbVie Medical Monitor. 7. Use of known strong inhibitors or inducers of cytochrome P450 (CYP) 3A within 2 weeks or 10 half-lives (if known), whichever was longer, of the respective medication/supplement, prior to initial dose of study drug. 8. Positive result of a urine drug screen at Screening for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol, with the exception of a positive result associated with documented short-term use or chronic stable use of a prescribed medication in that class. 9. Clinically significant abnormalities, other than HCV infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the investigator. 10. History of uncontrolled seizures, uncontrolled diabetes as defined by a haemoglobin A1C level > 8.0%, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years. 11. Any cause of liver disease other than chronic HCV infection, including but not limited to the following: • Hemochromatosis • Alpha-1 antitrypsin deficiency • Wilson's disease • Autoimmune hepatitis • Alcoholic liver disease • Non-alcoholic steatohepatitis • Drug-related liver disease 12. Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive 2D or RBV (GT4). 13. Current enrolment in another clinical study, previous enrolment in this study, or previous use of any investigational (including previous exposure to 2D) or commercially available

	6. Subjects had to be able to understand and adhere to the study visit schedule and all other protocol requirements. 7. BMI was from ≥ 18 to < 38 kg/m2. BMI was calculated as weight in kilograms (kg) divided by the square of height measured in meters (m). 8. Subject voluntarily signed and dated an ICF, approved by an IRB, prior to the initiation of any screening or study specific procedures. 9. Subject had plasma HCV RNA level > 10,000 IU/mL at Screening. 10. Chronic HCV GT4 (Groups 1, 4, 5 and 6) or GT1b (Groups 2, 3, 7 and 8) infection for at least 6 months prior to study screening. Chronic HCV infection was defined as one of the following: • Positive for anti-HCV antibody or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV antibody at the time of Screening; or • Positive for anti-HCV antibody and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrolment with evidence of chronic hepatitis C disease). In addition to Inclusion criteria 1 to 10, subjects enrolled in Sub-study 1 (subjects with HCV GT1b or GT4 infection, without cirrhosis) also had met the following criteria: 11. Per local standard practice, documented results of: • Liver biopsy within 24 months prior to screening or during screening demonstrating the absence of cirrhosis. • Only in the absence of a biopsy within the 24 months prior to screening or during screening: ○ a screening FibroTest score of ≤ 0.72 and AST to platelet ratio index (APRI) ≤ 2; or ○ a screening FibroScan® result of < 9.6 kPa.	anti-HCV agents other than IFN based therapy (IFN or pegIFN) and RBV in treatment-experienced subjects. 14. The use of colony stimulating factors, such as granulocyte colony stimulating factor (GCSF) or erythropoietin within 2 months of the Screening Period. 15. HCV genotype performed during screening indicating unable to genotype or co-infection with any other HCV genotype. 16. History of solid organ transplant. 17. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks prior to study drug administration. In addition to Exclusion criteria 1 through 17, subjects enrolling in Sub-study 1 (subjects with HCV GT1b or GT4 infection, without cirrhosis) must not have met the following criteria: 18. Clinically significant abnormal ECG, or ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 450 msec at Screening or Study Day 1 (prior to dosing). 19. Any current or past clinical evidence of cirrhosis such as ascites or oesophageal varices, or prior biopsy showing cirrhosis. 20. Screening laboratory analyses showing any of the following abnormal laboratory results: • ALT > 5 × ULN • AST > 5 × ULN • Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min • Albumin < lower limit of normal (LLN) • Prothrombin time (PT)/International normalised ration (INR) > 1.5. Subjects with a known inherited blood disorder and INR > 1.5 could have been enrolled with permission from the AbbVie Study Designated Physician • Haemoglobin < LLN

	Subjects with a non-qualifying FibroTest/APRI or FibroScan result were permitted enrolment only if they had a qualifying liver biopsy performed during screening.	• Platelets < 120,000 cells per mm3 for subjects with METAVIR score < 3 or Ishak score < 4 on a biopsy within the last 24 months; for subjects with METAVIR score of 3 or Ishak score of 4, platelets < LLN • Absolute neutrophil count (ANC) < 1500 cells/µL (< 1200 cells/µL for subjects of black/African descent) • Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN

6.3.4 **Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.**

Table 33: Characteristics of participants in the RCTs across randomised groups in patients with HCV GT1

Trial no. (acronym) Baseline characteristic	Randomised group X	Randomised group Y
SAPPHIRE-I (N=631) [31]	**3D + RBV (N=473)**	**Placebo (N=158)**
Male sex, n (%)	271 (57.3)	73 (46.2)
Race, n (%)		
White	428 (90.5)	144 (91.1)
Black	26 (5.5)	8 (5.1)
Other	19 (4.0)	6 (3.8)
Hispanic ethnic group, n (%)	27 (5.7)	5 (3.2)
Age, yr		
Mean	49.4	51.2
Range	18.0-70.0	21.0-70.0
BMI		
Mean	25.7	26.2
Range	18.0-38.4	18.5-39.4
Fibrosis score F2 or F3, n (%)	110 (23.3)	42 (26.6)
IL28B CC genotype, n (%)	144 (30.4)	50 (31.6)
HCV genotype, n (%)		
1a	322 (68.1)	105 (66.5)
1b	151 (31.9)	53 (33.5)
HCV RNA, log10IU/mL	6.40 ± 0.62	6.47 ± 0.65
SAPPHIRE-II (N =394) [32]	**3D + RBV (N=297)**	**Placebo (N=97)**
Male sex, n (%)	167 (56.2)	60 (61.9)
Race, n (%)		
White	269 (90.6)	86 (88.7)
Black	22 (7.4)	10 (10.3)
Asian	6 (2.0)	0
Hispanic or Latino ethnic group, n (%)		
Hispanic or Latino	22 (7.4)	3 (3.1)
Not Hispanic or Latino	275 (92.6)	94 (96.9)
Geographic region, n (%)		
North America	136 (45.8)	33 (34.0)
Europe	150 (50.5)	61 (62.9)
Australia or New Zealand	11 (3.7)	3 (3.1)

Age, yr		
Mean	51.7	54.9
Range	19.0-71.0	30.0-69.0
BMI		
Mean	26.3	26.4
Range	18.1-38.1	18.5-36.7
Fibrosis score F2 or F3, n (%)	95 (32.0)	32 (33.0)
IL28B CC genotype, n (%)	34 (11.4)	7 (7.2)
IP-10, no./total n (%)		
<600 ng/l	199/276 (72.1)	70/95 (73.7)
≥600ng/l	77/276 (27.9)	25/95 (26.3)
HCV genotype, n (%)		
1a	173 (58.2)	57 (58.8)
1b	123 (41.4)	40 (41.2)
HCV RNA, log10IU/mL		
Mean	6.55	6.52
Range	4.61-7.70	5.20-7.55
Type of prior response, n (%)		
Relapse	86 (29.0)	29 (29.9)
Partial response	65 (21.9)	21 (21.6)
Null response	146 (49.2)	47 (48.5)
TURQUOISE-II (N =390) [33]	**12 Weeks of 3D group (N=208)**	**24 weeks of 3D group (N=172)**
Male sex, n (%)	146 (70.2)	121 (70.3)
Race, n (%)		
White	199 (95.7)	161 (93.6)
Black	6 (2.9)	6 (3.5)
Asian	3 (1.4)	5 (2.9)
Hispanic or Latino ethnic group, n (%)	25 (12.0)	20 (11.6)
Age, yr (mean ± SD)	57.1 ± 7.0	56.5 ± 7.9
BMI, (mean ± SD)	27.9 ± 4.1	27.9 ± 4.3
HCV genotype, n (%)		
1a	140 (67.3)	121 (70.3)
1b	68 (32.7)	51 (29.7)
IL28B CC genotype, n (%)	35 (16.8)	34 (19.8)
HCV RNA, log10IU/mL	6.41± 0.62	6.53± 0.52
Type of prior response to PegIFN/RBV, n (%)		
Relapse	29/122 (23.8)	23/98 (23.5)
Partial response	18/122 (14.8)	13/98 (13.3)
Null response	75/122 (61.5)	62/98 (63.3)
Platelet count, $x10^{-9}$/litre		
Median	140.0	142.5
IQR	104.0-188.5	105.0-183.0
Serum albumin, g/litre		
Median	40	39

IQR	37-42	37-42
PEARL-II [34] (N=186)	**3D + RBV (N=91)**	**3D (N=95)**
Male sex, n (%)	45 (49.5)	57 (60.0)
Race, n (%)		
White	84 (92.3)	86 (90.5)
Black	3 (3.3)	6 (6.3)
Hispanic or Latino ethnic group, n (%)	4 (4.4)	2 (2.1)
Geographic region, n (%)		
North America	14 (15.4)	19 (20.0)
Europe	77 (84.6)	76 (80.0)
Age, yr mean ± SD	54.2 ± 10.9	54.2 ± 10.5
BMI, mean ± SD	26.2 ± 4.1	27.5 ± 4.3
IL28B CC genotype, n (%)	10 (11.0)	7 (7.4)
HCV RNA, log10IU/mL	6.56 ± 0.56	6.48 ± 0.53
Type of prior response to PegIFN/RBV, n (%)		
Relapse	33 (36.3)	35 (36.8)
Partial response	26 (28.6)	27 (28.4)
Null response	32 (35.2)	33 (34.7)
Baseline fibrosis stage, n (%)		
F0-F1	64 (70.3)	61 (64.2)
F2	13 (14.3)	21 (22.1)
F3	14 (15.4)	13 (13.7)
PEARL-III [35] (N=419)	**3D + RBV (N=210)**	**3D + placebo (N=209)**
Male sex, n (%)	106 (50.5)	86 (41.1)
Race, n (%)		
White	198 (94.3)	196/208 (94.2)
Black	10 (4.8)	10/208 (4.8)
Other	2 (1.0)	2/208 (1.0)
Hispanic ethnic group, n (%)	2 (1.0)	5 (2.4)
Age, yr mean ± SD	48.4 ± 11.9	49.2 ± 12.0
Geographic region, n (%)		
North America	48 (22.9)	47 (22.5)
Europe	162 (77.1)	162 (77.5)
BMI, mean ± SD	25.8 ± 3.8	26.1 ± 4.2
Baseline fibrosis stage n/N (%)		
F0-F1	150/210 (71.4)	141/208 (67.8)
F2	38/210 (18.1)	47/208 (22.6)
F3	22/210 (10.5)	20/208 (9.6)
IL28B CC genotype, n (%)	44 (21.0)	44 (22.1)
HCV RNA, log10IU/mL	6.29 ± 0.77	6.33 ± 0.67
HCV RNA, ≥ 800,000 IU/mL, n (%)	159 (75.7)	148 (70.8)
PEARL-IV [35]	**3D + RBV**	**3D + placebo**

(N=305)	(N=100)	(N=205)
Male sex, n (%)	70 (70.0)	129 (62.9)
Race, n (%)		
White	86 (86.0)	171 (83.4)
Black	10 (10.0)	26 (12.7)
Other	4 (4.0)	8 (3.9)
Hispanic ethnic group, n (%)	10 (10.0)	18 (8.8)
Age, yr mean ± SD	51.6 ± 11.0	51.4 ± 10.6
Geographic region, n (%)		
North America	92 (92.0)	186 (90.7)
Europe	8 (8.0)	19 (9.3)
BMI, mean ± SD	26.9 ± 4.0	26.7 ± 4.3
Baseline fibrosis stage n/N (%)		
F0-F1	63/100 (63.0)	132/205 (64.4)
F2	21/100 (21.0)	35/205 (17.1)
F3	16/100 (16.0)	38/205 (18.5)
IL28B CC genotype, n (%)	31 (31.0)	63 (30.7)
HCV RNA, log10IU/mL	6.64 ± 0.50	6.53 ± 0.68
HCV RNA, ≥ 800,000 IU/mL, n (%)	92 (92.0)	172 (83.9)
AVIATOR [36] (n=571)	**Treatment naïve (n=438)**	**Patients without a response to prior therapy (n=133)**
Male sex, n (%)	232 (53)	82 (62)
Age, yr mean ± SD	50.1 ± 10.2	51.1 ± 11.4
Black race, n (%)	60 (14)	18 (14)
Hispanic ethnic group, n (%)	33 (8)	13 (10)
HCV sub-genotype 1a, n (%)	297 (68)	
IL28B CC genotype, n (%)	124 (28)	4 (3)
HOMA-IR ≥ 3 n/N (%)	98/385 (25)	34/112 (30)
IP-10 ≥ 600 ng/mL, n/N (%)	101/428 (24)	53/128 (41)
Fibrosis score ≥ F2, n (%)	127 (29)	66 (50)
HCV RNA, , log10IU/mL	6.53 ± 0.55	6.64 ± 0.45
Single arm studies		
M14-103 [37]		
Male sex, n (%)	25 (65.8)	
Age, yr mean ± SD	48.2 ± 11.00	
Black race, n (%)	2 (5.3)	
Hispanic ethnic group, n (%)	1 (2.6)	
Weight, kg mean ± SD	79.7 ± 13.20	
HCV sub-genotype 1a, n (%)	32 (84.2)	
IL28B CC genotype, n (%)	12 (31.6)	
HCV RNA, log10IU/mL	6.58 ± 0.70	
IP-10 ≥ 600 ng/mL, n	6 (15.8)	
Type of prior response to PegIFN/RBV, n (%)		

Naive	36 (94.7)
Relapser	1 (2.6)
Null response	1 (2.6)
Baseline fibrosis stage n/N (%)	
F0-F1	30 (78.9)
F2	6 (15.8)
F3	2 (5.3)
History of diabetes, yes, n (%)	0 (0)
History of depression/bipolar disorder, yes, n (%)	17 (44.7)

Table 34: HCV GT4 Patient characteristics from PEARL-I

Trial no. (acronym) Baseline characteristic	Randomised group X	Randomised group Y	Group Z
PEARL-I [39]	12 weeks 2D		12 weeks 2D + RBV
	Group 1 Tx naïve N=44	Group 4 Tx naïve N=42	Group 6 Tx-experienced N=49
Male sex, n (%)	24 (54.5)	28 (66.7)	36 (73.5)
Age, yr mean ± SD	48.9 ± 10.03	44.2 ± 12.67	50.9 ± 10.13
Black race, n (%)	6 (13.6)	3 (7.1)	3 (6.1)
Hispanic ethnic group, n (%)	4 (9.1)	1 (2..4)	3 (6.1)
Weight, kg mean ± SD	72.6 ± 15.25	74.3 ± 13.04	79.4 ± 14.58
Geographic region, n (%)			
North America	6 (13.6)	6 (14.3)	7 (14.3)
Europe	38 (86.4)	36 (85.7)	42 (85.7)
HCV sub-genotype, n (%)			
4a/c/d	21 (47.7)	26 (61.9)	32 (65.3)
4e	0	0	1 (2.0)
4f	3 (6.8)	3 (7.1)	0
4h	1 (2.3)	0	1 (2.0)
4 [a]	19 (43.2)	13 (31.0)	15 (30.6)
IL28B CC genotype, n (%)	12 (27.3)	11 (26.2)	6 (12.2)
HCV RNA, log10IU/mL mean ± SD	6.10 ± 0.58	6.11 ± 0.59	6.27 ± 0.49
HCV RNA, ≥ 800,000 IU/mL, n (%)	27 (61.4)	30 (71.4)	37 (75.5)
Type of prior response to PegIFN/RBV, n (%)			
Partial responder	NA	NA	9 (18.4)
Relapser	NA	NA	17 (34.7)
Null response	NA	NA	23 (46.9)
Baseline fibrosis stage n/N (%)			
F0-F1	38 (86.4)	33 (78.6)	33 (67.3)
F2	4 (9.1)	6 (14.3)	11 (22.4)
F3	2 (4.5)	2 (4.8)	5 (10.2)
F4	0	1 (2.4)	0

Outcomes

6.3.5 **Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT**

Table 35 provides details of the pre-specified primary and secondary outcomes in the AbbVie HCV clinical trial programme. The primary outcome for all the trials was sustained virologic response (SVR) - defined as an HCV RNA level <25 IU per millilitre at 12 weeks after the end of treatment. SVR is deemed equivalent to cure and is the gold standard in clinical practice in the UK.

Pre-specified secondary outcome measures include but are not limited to the following: liver function tests; non-inferiority and superiority to historical telaprevir SVR rates; SVR characterised by different sub-groups e.g. sub-genotype or different treatment periods; evaluation of any virologic failure during treatment and post-treatment relapse.

In addition to the pre-specified secondary outcomes, all the trials also collected exploratory patient reported outcome data – specifically the HCV-PRO, the EQ-5D-5L and the SF-36. The SF-36 is a well-used and validated generic measure of HRQoL. The EQ-5D-5L is an expansion of the well-used and validated EQ-5D-3L; it is an expanded version because each of the 5 domains has five levels of severity rather than three, such that it is more sensitive to smaller changes in HRQOL. The disadvantage of its use currently is that in order to obtain index values for HRQoL an algorithm to 'cross-walk' the 5L to individual countries 3L values has to be used. Several of the countries included in the various studies do not have country specific cross-walk data-sets, and where this is the case the US cross-walk has been used. The data presented in Section 6.5 comprise a mixture of different countries algorithms, and therefore are difficult to interpret because it's likely that the values will be driven by the proportion the individual country is represented by in the sample, rather than actual differences in HRQoL because of the differences in individual countries' tariffs. For the economic modelling, see Section 7.4, the UK cross-walk has been applied to the entire data set to ensure consistency in the methodology of

obtaining utility values, and thus any differences can be attributed to an actual change in HRQoL rather than sampling of country-specific tariff differences.

The studies also collected data from a newly developed patient reported outcome tool specifically for HCV (HCV-PRO).[40] The 16 item questionnaire focuses on aspects of physical health, emotional health, productivity, social interactions, intimacy and perception. The validity, responsiveness and identification of the minimally important difference in score have been tested in trials.[41]

Finally, measurements of treatment compliance were also analysed but this was not a pre-specified outcome.

Table 35: Primary and secondary outcomes of the AbbVie RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures/ Exploratory outcomes and measures	Reliability/validity/ current use in clinical practice
SAPPHIRE-I [31]	Sustained virological response (SVR) –defined as an HCV RNA level <25 IU per millilitre at 12 weeks after the end of treatment.	SVR is the primary aim of treatment in clinical practice. SVR12 is the established appropriate endpoint for regulatory approval and is accepted by EMA and the FDA. SVR12 is specified in the scope as a valid endpoint.	**Secondary outcomes:** • Normalisation of ALT, • SVR at post-treatment week 12 according to HCV genotype (1a or 1b), • virologic failure during treatment, • post-treatment relapse. **Exploratory outcomes:** • HCV-PRO • EQ-5D-5L • SF-36	• Liver function tests form an integral part of the care of HCV infected patients to monitor any change in liver function e.g. progression of fibrosis. • For the small proportion of patients who might experience virologic failure or relapse post-treatment it is important to characterise the reasons why to determine subsequent treatment options.
SAPPHIRE-II [32]	Sustained virological response (SVR) –defined as an HCV RNA level <25 IU per millilitre at 12 weeks after the end of treatment.	SVR (defined as undetectable HCV RNA) is the primary aim of treatment in clinical practice. SVR12 is the established appropriate endpoint for regulatory approval and is accepted by EMA and the FDA. SVR12 is specified in the scope as a valid endpoint.	**Secondary outcomes:** • Normalisation of ALT, • SVR at post-treatment week 12 according to HCV genotype (1a or 1b), • virologic failure during treatment, • post-treatment relapse. **Exploratory outcomes:** • HCV-PRO • EQ-5D-5L • SF-36	• Liver function tests form an integral part of the care of HCV infected patients to monitor any change in liver function e.g. progression of fibrosis. • For the small proportion of patients who might experience virologic failure or relapse post-treatment it is important to characterise the reasons why to determine subsequent treatment options.
TURQUOISE-II [33]	Sustained virological response (SVR) –defined as an HCV RNA level <25 IU per millilitre at 12 weeks after the end of	SVR (defined as undetectable HCV RNA) is the primary aim of treatment in clinical practice. SVR12 is the established appropriate endpoint for regulatory approval and is	**Secondary outcomes:** • Comparison of SVR12 rates between the 12 and 24 week treatment arms • Virologic failure during treatment	For the small proportion of patients who might experience virologic failure or relapse post-treatment it is important to characterise the reasons why to determine subsequent

	treatment.	accepted by EMA and the FDA. SVR12 is specified in the scope as a valid endpoint.	• Post-treatment relapse **Exploratory outcomes:** • HCV-PRO • EQ-5D-5L • SF-36	treatment options.
PEARL-II [34]	Sustained virological response (SVR) –defined as an HCV RNA level <25 IU per millilitre at 12 weeks after the end of treatment.	SVR (defined as undetectable HCV RNA) is the primary aim of treatment in clinical practice. SVR12 is the established appropriate endpoint for regulatory approval and is accepted by EMA and the FDA. SVR12 is specified in the scope as a valid endpoint.	**Secondary outcomes:** • to compare the percentage of subjects with a decrease in haemoglobin to below the lower limit of normal (LLN) at the end of treatment between treatment arms +/- RBV; • to show the superiority in SVR12 rates of 12 weeks of treatment with 3D with and without RBV to the historical SVR rate of telaprevir plus PegIFN/RBV therapy, • to demonstrate the non-inferiority in SVR12 rates of 12 weeks of treatment with 3D without RBV to 12 weeks of treatment with 3D + RBV; • Virologic failure during treatment • post-treatment relapse. **Exploratory outcomes:** • HCV-PRO • EQ-5D-5L • SF-36	• For the small proportion of patients who might experience virologic failure or relapse post-treatment it is important to characterise the reasons why to determine subsequent treatment options. • It is important to assess the effect of 3D monotherapy vs 3D + ribavirin on known side effects of ribavirin such as anaemia.
PEARL-III [35]	Sustained virological response (SVR) –defined as an HCV RNA level	SVR (defined as undetectable HCV RNA) is the primary aim of treatment in clinical practice.	**Secondary outcomes:** • to demonstrate the non-inferiority in SVR12 rates of	• For the small proportion of patients who might experience virologic failure or relapse post-

	<25 IU per millilitre at 12 weeks after the end of treatment.	SVR12 is the established appropriate endpoint for regulatory approval and is accepted by EMA and the FDA. SVR12 is specified in the scope as a valid endpoint.	12 weeks of treatment with 3D without RBV to 12 weeks of treatment with 3D + RBV; • to compare the percentage of subjects with a decrease in haemoglobin to below the lower limit of normal (LLN) at the end of treatment between treatment arms; • to show the superiority in SVR12 rates of 12 weeks of treatment with 3D with and without RBV to the historical SVR rate of telaprevir plus PegIFN/RBV therapy; and • virologic failure during treatment • post-treatment relapse **Exploratory outcomes:** • HCV-PRO • EQ-5D-5L • SF-36	treatment it is important to characterise the reasons why to determine subsequent treatment options. • It is important to assess the effect of 3D monotherapy vs 3D + ribavirin on known side effects of ribavirin such as anaemia.
PEARL-IV [35]	Sustained virological response (SVR) –defined as an HCV RNA level <25 IU per millilitre at 12 weeks after the end of treatment.	SVR (defined as undetectable HCV RNA) is the primary aim of treatment in clinical practice. SVR12 is the established appropriate endpoint for regulatory approval and is accepted by EMA and the FDA. SVR 12 is specified in the scope as a valid endpoint.	**Secondary outcomes:** • to demonstrate the non-inferiority in SVR12 rates of 12 weeks of treatment with 3D without RBV to 12 weeks of treatment with 3D + RBV; • to compare the percentage of subjects with a decrease in haemoglobin to below the lower limit of normal (LLN) at the end of treatment between treatment arms; • to show the superiority in	• For the small proportion of patients who might experience virologic failure or relapse post-treatment it is important to characterise the reasons why to determine subsequent treatment options. • It is important to assess the effect of 3D monotherapy vs 3D + ribavirin on known side effects of ribavirin such as anaemia.

			SVR12 rates of 12 weeks of treatment with 3D with and without RBV to the historical SVR rate of telaprevir plus PegIFN/RBV therapy; and • virologic failure during treatment • post-treatment relapse **Exploratory outcomes:** • HCV-PRO • EQ-5D-5L • SF-36	

AVIATOR [36]	Sustained virological response (SVR) –defined as an HCV RNA level <25 IU per millilitre at 24 weeks after the end of treatment.	SVR (defined as undetectable HCV RNA) is the primary aim of treatment in clinical practice. This study used SVR24 rather than SVR12. Collection of SVR 24 weeks post end-of-treatment was the measurement time point used for the traditional HCV therapies (PegIFN/RBV, telaprevir and boceprevir), which is still valid but SVR12 is now more widely used.	**Secondary outcomes:** To compare the percentage of subjects achieving SVR24: • who had been treated with 3 DAAs with RBV for 8 versus 24 weeks (treatment-naïve subjects) and for 12 weeks versus 24 weeks (treatment-naïve and null responder subjects); • who had been treated with 2 DAAs (ABT-450/r and ABT-333) with RBV for 12 weeks versus 3 DAAs with RBV for 12 weeks (treatment-naïve subjects); • who had been treated with 2 DAAs (ABT-450/r and ABT-267) with RBV for 12 week versus 3 DAAs with RBV for 12 weeks (treatment-naïve and null responder subjects); • who had been treated with 3 DAAs with RBV for 12 weeks versus 3 DAAs without RBV for 12 weeks (treatment-naïve subjects); • among treatment-naïve versus null responder subjects who had been treated with 3 DAAs with RBV for 12 or 24 weeks at different doses of ABT-450/r (100/100 mg, and 150/100	

			mg), and • to examine any emerged or enriched mutations post-baseline by mixed population and/or clonal sequencing. **Exploratory outcomes:** • HCV-PRO • EQ-5D-5L • SF-36	

M14-103 [37]	Sustained virological response (SVR) –defined as an HCV RNA level <25 IU per millilitre at 12 weeks after the end of treatment.	SVR (defined as undetectable HCV RNA) is the primary aim of treatment in clinical practice. SVR12 is the established appropriate endpoint for regulatory approval and is accepted by EMA and the FDA. SVR 12 is specified in the scope as a valid endpoint.	**Secondary outcomes:** • virologic failure during treatment • post-treatment relapse • characterise 3D's pharmacokinetics in HCV-infected subjects on methadone or buprenorphine therapies. **Exploratory outcomes:** • HCV-PRO • EQ-5D-5L • SF-36	• For the small proportion of patients who might experience virologic failure or relapse post-treatment it is important to characterise the reasons why to determine subsequent treatment options. • There is a clinical need to ensure that there are no unexpected drug-drug interactions between 3D and opioid replacement therapy.
Trial no. (acronym)	**Primary outcome(s) and measures**	**Reliability/validity/ current use in clinical practice**	**Secondary outcome(s) and measures/ Exploratory outcomes and measures**	**Reliability/validity/ current use in clinical practice**
PEARL-I [39]	Sustained virological response (SVR) –defined as an HCV RNA level <25 IU per millilitre at 12 weeks after the end of treatment.	SVR (defined as undetectable HCV RNA) is the primary aim of treatment in clinical practice. SVR12 is the established appropriate endpoint for regulatory approval and is accepted by EMA and the FDA. SVR 12 is specified in the scope as a valid endpoint.	**Secondary outcomes:** • virologic failure during treatment • post-treatment relapse • percentage of subjects with SVR24 **Exploratory outcomes:** • HCV-PRO • EQ-5D-5L	For the small proportion of patients who might experience virologic failure or relapse post-treatment it is important to characterise the reasons why to determine subsequent treatment options.

Statistical analysis and definition of study groups

6.3.6 **State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.**

Table 36 summarises the primary hypotheses for the trials in the AbbVie clinical programme, as well as details of the power calculations, a description of the intent-to-treat population and whether a per protocol analysis was undertaken.

It is important to note that for the following studies SAPPHIRE-I, PEARL-II, PEARL-III, and TURQUOISE-II that 5 subjects (1 subject, 1 subject, 2 subjects and 1 subject respectively) were not available to have their 12 week post-treatment SVR status recorded prior to primary endpoint data lockdown. As such the CSRs and publications in *NEJM* for these trials record these patients as non-responders as per the SAP for missing data. However, at subsequent clinical visits following primary endpoint data lock-down, SVR status was collected. As per the SAP and per trial protocols, backward imputation of SVR data was possible. Therefore, the SVR data presented in Section 6.5 are slightly different from the SVR data reported in CSRs and the NEJM publications. The US FDA filing and US label as well as the draft SPC submitted to EMA both include the revised data.

Table 36: Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
SAPPHIRE-I [31]	The primary objectives of this study were to show the non-inferiority in SVR12 rates after 12 weeks of treatment with 3D + RBV to the historical SVR rate of telaprevir plus PegIFN and RBV therapy and to assess the safety of 3D versus placebo for 12 weeks in treatment naive HCV GT 1-infected adults without cirrhosis.	See Table 26 for details	This study was planned to enrol 600 patients in a 3:1 ratio to 3D + RBV or placebo (450 patients randomised to active drug and 150 patients randomised to placebo). The primary efficacy endpoint of SVR12 was assessed within the patients randomised to Arm A. With a sample size of 450 patients and assuming that 92% of the patients in Arm A will achieve SVR12, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 95% lower confidence bound greater than 70% and greater than 90% power to demonstrate superiority with a 2-sided 95% lower confidence bound greater than 80%.	Each subject had the right to withdraw from the study at any time. In addition, the investigator could have discontinued a subject from the study at any time if the investigator considered it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol. No adjustment for dropout was applicable because patients without data at Post-Treatment Week 12 (after imputing) were counted as failures for SVR12.
SAPPHIRE-II [32]	The primary objectives of this study were to compare the percentage of subjects achieving SVR12 after 12 weeks of treatment with 3D + RBV to the historical SVR rate of telaprevir plus PegIFN and RBV therapy and to assess the safety of 3D versus placebo for 12 weeks in PegIFN/RBV treatment-experienced HCV GT1-infected adults without cirrhosis.	See Table 26 for details	This study was planned to enrol 400 patients in a 3:1 ratio to 3D + RBV or placebo (300 patients randomised to active drug and 100 patients randomised to placebo). The primary efficacy endpoint of SVR12 was assessed within the patients randomised to active drug. With a sample size of 300 patients and assuming that 85% of the patients in randomised to active regimen would achieve SVR12, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 95% lower confidence bound greater than 60% and greater than 90% power to demonstrate superiority with a 2-sided 95% lower confidence bound greater than 70%. No adjustment for dropout was	Each subject had the right to withdraw from the study at any time. In addition, the investigator could have discontinued a subject from the study at any time if the investigator considered it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol. No adjustment for dropout was applicable because patients without data at Post-Treatment Week 12 (after imputing) were counted as failures for SVR12.

			applicable because patients without data at Post-Treatment Week 12 (after imputing) were counted as failures for SVR12.	

TURQUOISE-II [33]	The primary objectives of this study were to assess the safety and compare the SVR12 rates for 12 or 24 weeks of treatment with 3D + RBV to the historical SVR rate of telaprevir plus PegIFN and RBV therapy and to assess the safety of 3D versus placebo for 12 weeks in PegIFN/RBV treatment-experienced HCV GT1-infected adults without cirrhosis.	See Table 27 for details	With a total sample size of about 380 subjects and assuming that 68% of the patients in each arm will achieve SVR12, this study had greater than 90% power to demonstrate non-inferiority with a 2-sided 97.5% lower confidence bound greater than 43%, and 90% power to demonstrate superiority with a 2- sided 97.5% lower confidence bound greater than 54% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority using EAST 5.4). For the comparison of SVR12 between treatment arms, a total sample size of approximately 380 subjects provided 80% power using Fisher's exact test with a 2-sided significance level of 0.05 to detect a difference of approximately 13% assuming underlying SVR12 rates of 68% and 81% in the 12- and 24- week arms, respectively. If the SVR12 rates were higher, then there was 80% power to detect a difference of approximately 10.5% with SVR12 rates of 80.5% and 91% in the 12- and 24-week arms, respectively.	Each subject had the right to withdraw from the study at any time. In addition, the investigator could have discontinued a subject from the study at any time if the investigator considered it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol. There was no adjustment for dropout because patients with no data at post-treatment week 12 (after imputing) were counted as failures for SVR12.
PEARL-II [34]	The primary objectives of this study were to evaluate the safety of 12 weeks of treatment with 3D with and without RBV and to show the non-inferiority in SVR12 rates in both arms to the historical SVR rate of telaprevir plus PegIFN	See Table 28 for details	PEARL-II planned to enroll 210 patients in a 1:1 ratio to 3D with RBV or without RBV, so that at least 200 patients were dosed with the co-formulated tablets of ABT-450/ritonavir/ombitasvir. Based on a 2-sided significance level of 0.05, and an underlying SVR12 rate of 82% or higher in Group 1 and 82% or higher in Group 2, a sample size of 90 patients per group provides > 90% power to demonstrate non-	Each subject had the right to withdraw from the study at any time. In addition, the investigator could have discontinued a subject from the study at any time if the investigator considered it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol. No adjustment for dropout was applicable

	and RBV therapy.		inferiority of the ABT-450/ritonavir/ombitasvir + dasabuvir regimen ± RBV to the historical SVR rate for telaprevir plus PegIFN and RBV therapy (64%).	because patients without data at Post-Treatment Week 12 (after imputing) are counted as failures for SVR12.

PEARL-III [35]	The primary objectives of this study were to compare the safety of 3D administered with and without RBV for 12 weeks and to show the non-inferiority in SVR12 of 12 weeks of treatment with 3D administered with and without RBV compared with the historical SVR rate of telaprevir plus PegIFN and RBV therapy in treatment-naïve HCV sub-genotype 1b-infected adults without cirrhosis.	See Table 28 for details	PEARL-III planned to enrol 400 patients in a 1:1 ratio to 3D with ribavirin or placebo for ribavirin (200 patients randomized to active drug + ribavirin and 200 patients randomised to active drug + placebo). Randomisation was stratified by IL28B genotype (CC vs. non-CC). Based on a 2-sided significance level of 0.05, and an underlying SVR12 rate of 92% or higher in each arm, a sample size of 200 patients per treatment group provided > 95% power to demonstrate non-inferiority each regimen to the historical SVR rate for telaprevir plus PegIFN and ribavirin therapy (84%), and it provided > 90% power to demonstrate superiority of each regimen to the historical SVR rate for telaprevir plus PegIFN and ribavirin therapy (84%). The planned sample size provided >95% to demonstrate non-inferiority of the regimen with placebo to the regimen with ribavirin, based on a -10.5% non-inferiority margin.	No adjustment for dropout was applicable because patients without data at Post-Treatment Week 12 (after imputing) were considered as failures for SVR12.
PEARL-IV [35]	The primary objectives of this study were to compare the safety of 3D administered with and without RBV for 12 weeks and to show the non-inferiority in SVR12 rates of 12 weeks of treatment with 3D administered with and without RBV compared with the historical SVR rate of telaprevir plus PegIFN and RBV therapy in	See Table 29 for details	PEARL-IV planned to enrol 300 patients in a 1:2 ratio to receive 3D with ribavirin or 3D plus placebo for ribavirin (100 patients randomised to active drug + ribavirin and 200 patients randomised to active drug + placebo). Randomisation was stratified by IL28B genotype (CC vs. non-CC). Based on a 2-sided significance level of 0.05, and an underlying SVR12 rate of 90% or higher in the treatment group receiving ribavirin and 85% or higher in the treatment group without ribavirin, a sample size of 100 patients for the treatment group receiving ribavirin and 200 patients in for the group	No adjustment for dropout was applicable because patients without data at Post-Treatment Week 12 (after imputing) were considered as failures for SVR12.

	treatment-naïve HCV sub-genotype 1a-infected adults without cirrhosis.		without ribavirin provided > 95% power to demonstrate non-inferiority of each regimen to the historical SVR rate for telaprevir plus PegIFN and ribavirin therapy (75%), and it provided > 90% power to demonstrate superiority of each regimen to the historical SVR rate for telaprevir plus PegIFN and ribavirin therapy (75%).	

AVIATOR [36]	The primary objectives of this study were to assess the safety of all treatment regimens, and to compare the percentage of subjects achieving SVR24 following 8 weeks of treatment with 3D + RBV versus 12 weeks of treatment with 3D + RBV in HCV genotype 1-infected treatment-naïve adults.	See Table 30 for details.	For the primary efficacy endpoint of SVR24, if we assume a rate of SVR24 of 66% in Group A and 90% in Group G, 80 subjects in Group A and 40 subjects in Group G would provide 80% power using Fisher's exact test with a two-sided significance level of 0.05 to detect a difference of approximately 24% between the 2 groups. On the other hand, when comparing the comparable groups in Cohort 1 (Groups F, G, H, and I) and Cohort 2 (Groups K, L, M, and N), 160 subjects in the first set of groups and 80 subjects in the second set of groups provide > 80% power to detect a difference of approximately 17% in SVR24 rates (87% versus 70%) between the 2 sets of groups.	Interim analyses of all data were planned after all subjects completed treatment or prematurely discontinued study drug, after the last subject reached Post-Treatment Week 12 or prematurely discontinued the study, and after the last subject reached Post-Treatment Week 24 or prematurely discontinued the study. For each of these overall interim analyses, appropriate database clean-up procedures were performed. No statistical adjustment was employed due to these analyses, as this was an open-label study.
M14-103 [37]	The primary objectives of this study were to assess the safety and the percentage of subjects achieving a SVR12 treatment with 3D + RBV for 12 weeks in HCV genotype 1-infected adults who were on a stable opioid replacement therapy with methadone or buprenorphine ± naloxone.	See Table 30 for details.	Enrolment of approximately 40 subjects in this study was planned. With a sample size of 40 subjects and an observed SVR12 rate of 80%, the 2-sided 95% CI using the normal approximation of the binomial would be (67.6%, 92.4%) with a width of 24.8%. The 2-sided 95% CIs using the normal approximation of the binomial for various SVR12 rates given a sample size of 40 subjects are presented below: **SVR12 rate** — **95% CI** 60% — (44.8%, 75.2%) 70% — (55.8%, 84.2%) 80% — (67.6%, 92.4%)	Subjects who did not have data at Post-Treatment Week 12 (after performing the described imputation) counted as failures for SVR12, so no adjustment for dropout was applicable.
Trial no. (acronym)	**Hypothesis objective**	**Statistical analysis**	**Sample size, power calculation**	**Data management, patient withdrawals**
PEARL-I [39]	The primary objectives	See Table	For the primary efficacy endpoint of SVR12,	No data was imputed for any efficacy or safety

	were to assess the safety and efficacy (SVR12) of 2D: • among treatment-naïve and prior PegIFN/RBV null responder HCV GT1b subjects without cirrhosis and among treatment-naïve and PegIFN/RBV treatment-experienced HCV GT1b subjects with compensated cirrhosis. • with or without RBV among treatment-naïve and PegIFN/RBV treatment-experienced HCV GT4-infected subjects.	31 for details of statistical analysis	assuming rates of 70% in Group 1 and 95% in Group 4, 40 subjects per group would provide approximately 80% power using Fisher's exact test with a 2-sided significance level of 0.05 to detect a difference of approximately 25% between the HCV GT4-infected treatment-naïve subjects treated with either 2D + RBV or 2D alone for 12 weeks.	analysis except for the PRO questionnaires and for all analyses of SVR, and rapid virologic response (RVR). For HCV-PRO, if a respondent answers at least 12 of the 16 items, the missing items were imputed with the average score of the answered items. In cases where the respondent did not answer 5 or more items, the total score was considered missing. For EQ-5D-5L, no imputation was performed for missing items. No adjustment for dropout was applicable because patients without data at Post-Treatment Week 12 (after imputing) were considered as failures for SVR12.

6.3.7 **Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.**

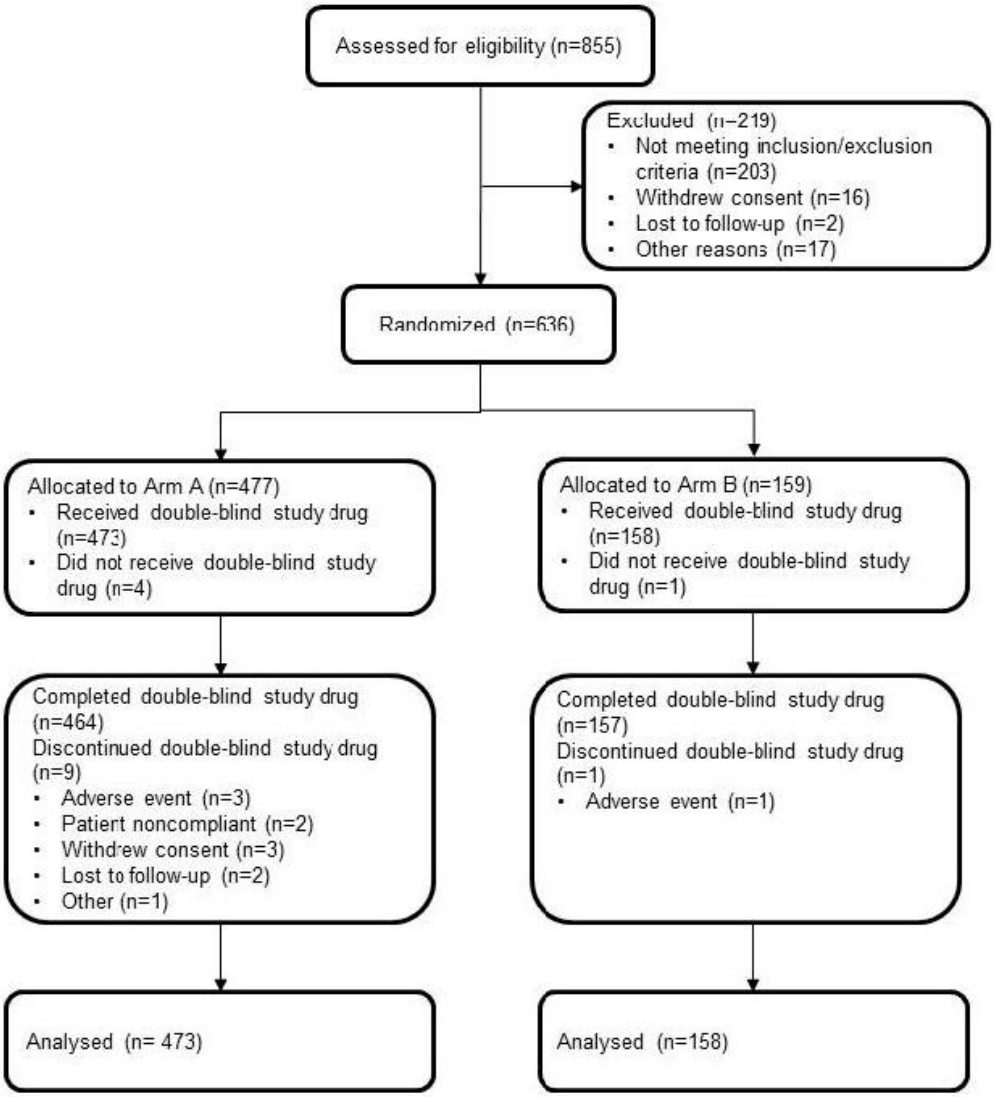
Pre-planned subgroup analyses were undertaken in all studies to assess any differences in the percentage of subjects with SVR12 according to various pre-specified demographic and baseline clinical characteristics e.g. sex, age, race, ethnicity, BMI, IL28B genotype, baseline HCV RNA level, baseline fibrosis stage, etc. Results are presented in Section 6.5 for each study.

Participant flow

6.3.8 **Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.**

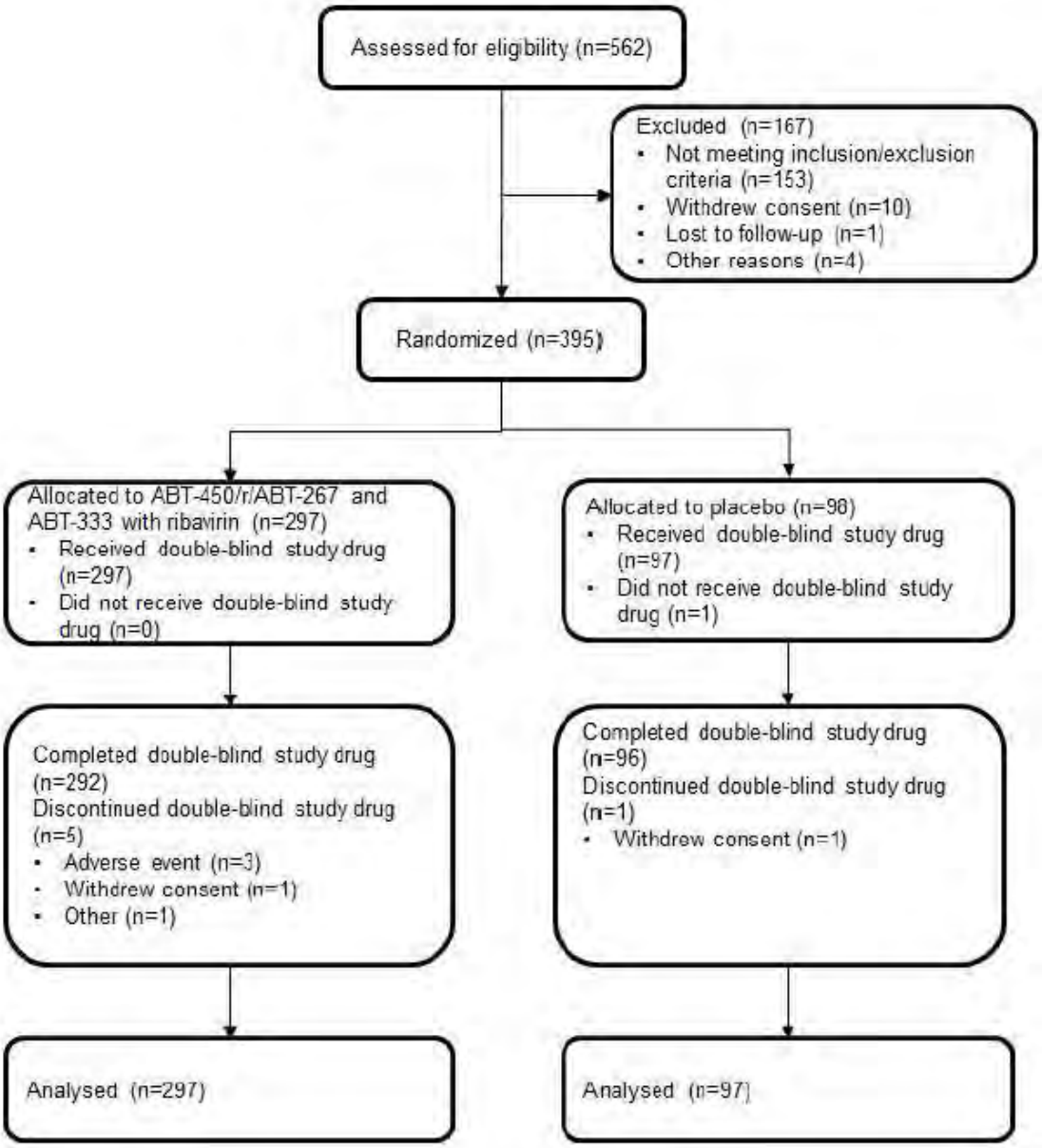
Figure 5 to Figure 11 below detail the patient disposition for each phase III trial in AbbVie's HCV GT1 clinical trial programme and also the phase II trial - PEARL-I in HCV GT4 patients:

Figure 5: HCV GT1 - SAPPHIRE-I patient disposition



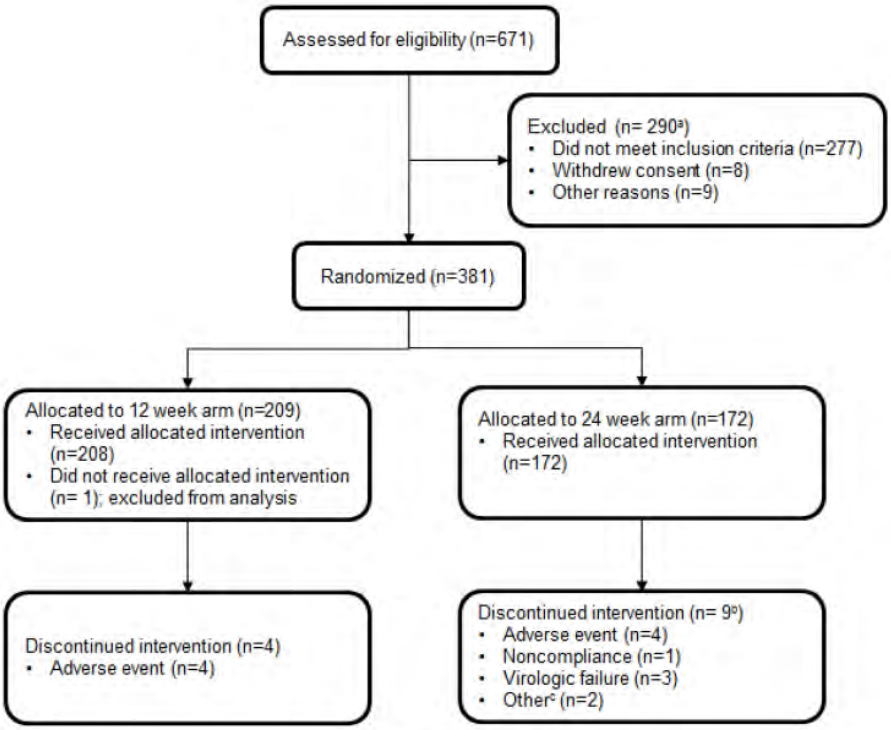
Source: Figure S1, supplementary appendix of Feld et al *NEJM* 2014.[31]
Treatment naïve patients with chronic HCV genotype 1 infection were assessed for eligibility and randomised to receive either ABT450/r/ABT-267 and ABT-333 with ribavirin or placebo during the double blind period.

Figure 6: HCV GT1 - SAPPHIRE-II patient disposition



Source: Figure S1, supplementary appendix of Zeuzem et al *NEJM* 2014.[32]
PegIFN + RBV treatment-experienced patients with chronic HCV genotype 1 infection were assessed for eligibility and randomised to receive either ABT450/r/ABT-267 and ABT-333 with ribavirin or placebo during the double blind period.

Figure 7: HCV GT1 - TURQUOISE-II patient disposition



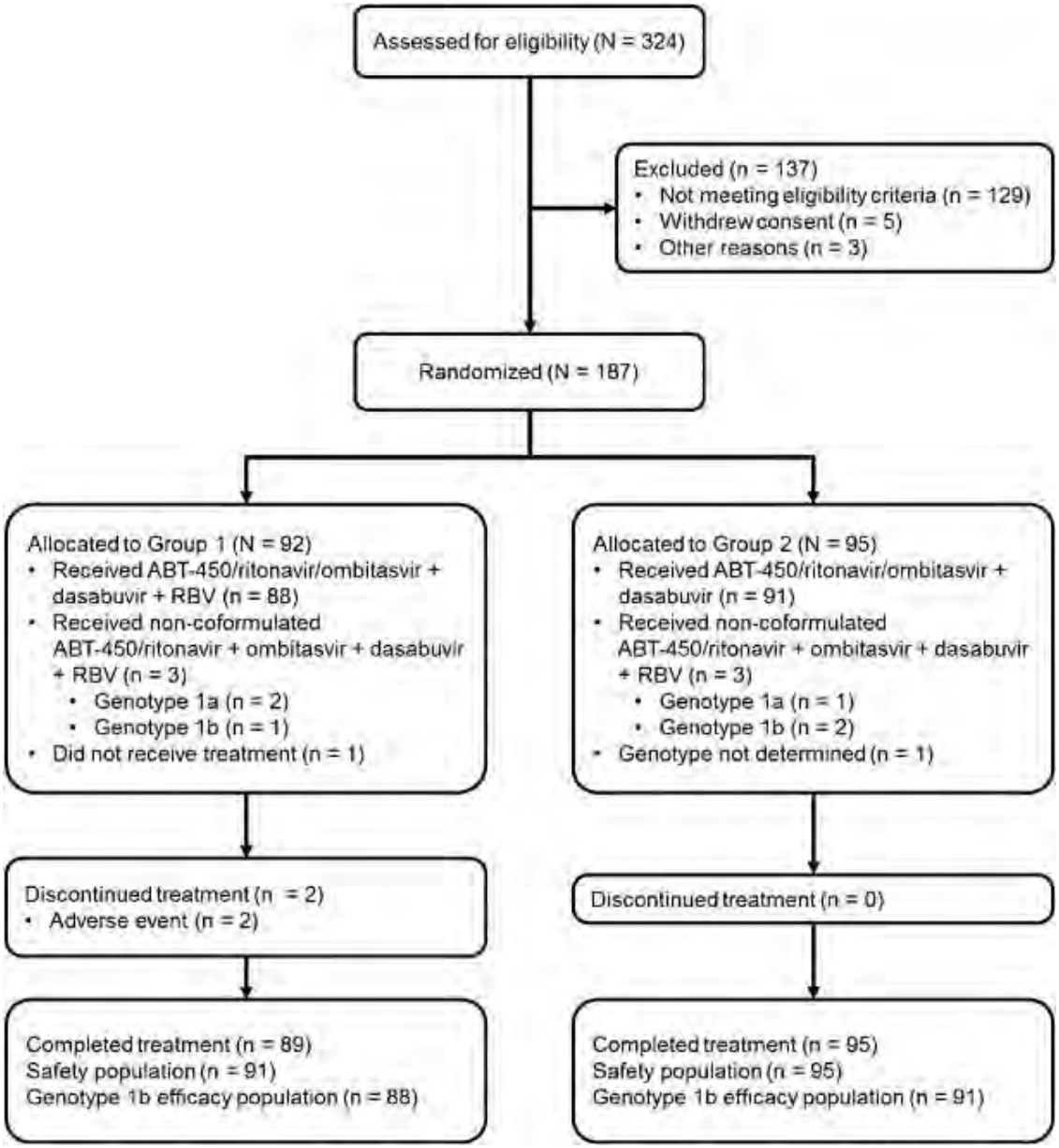
[a] There could be more than one reason for screen failure.

[b] There could be more than one reason for discontinuation.

[c] Other reasons for discontinuation: 1 patient was incarcerated; 1 patient discontinued for personal issues unrelated to study drug. Both patients were considered treatment failures in the intent-to-trea analysis.

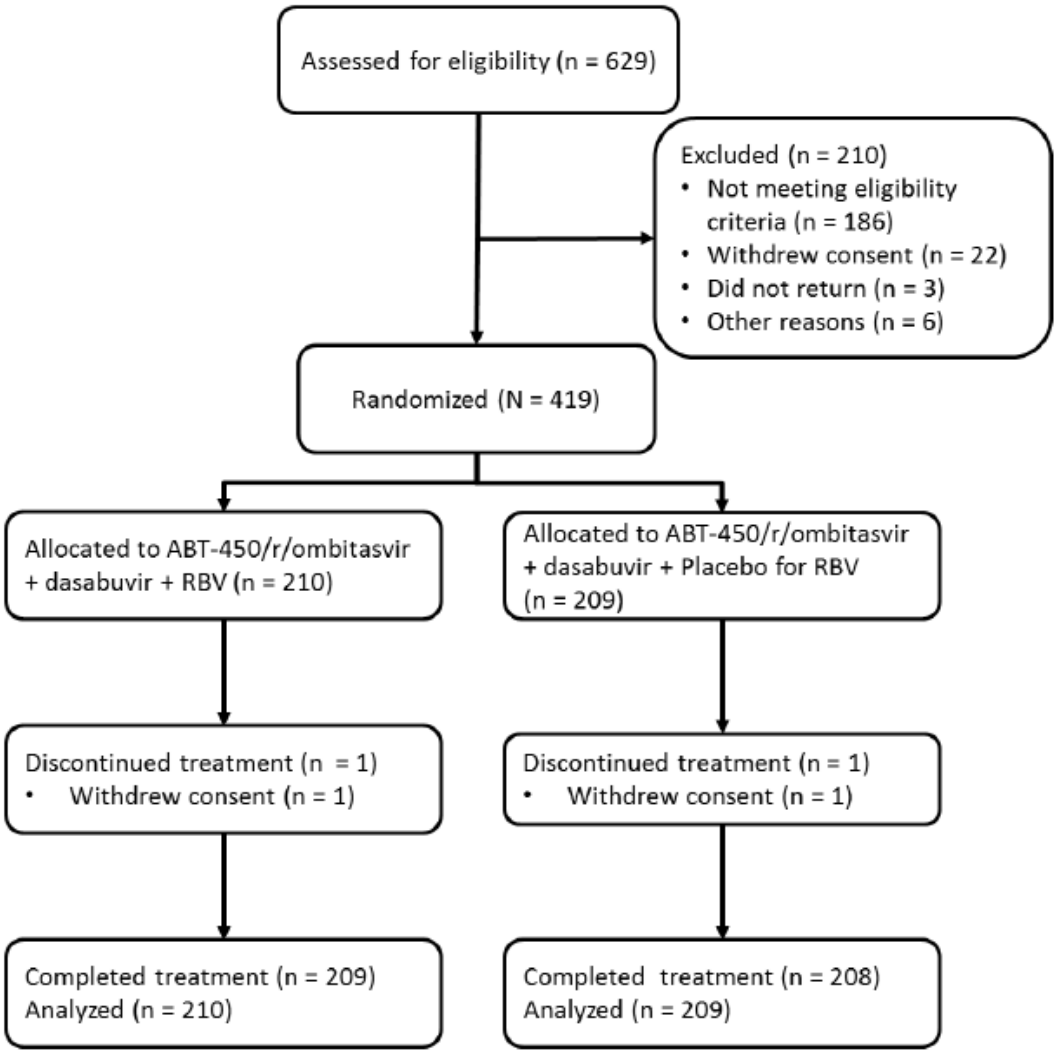
Source: Figure S3, supplementary appendix of Poordad *et al NEJM* 2014.[33]

Figure 8: HCV GT1b - PEARL-II patient disposition



Source: Supplementary Consort Flow Chart 1. Andreone et al, Gastroenterology 2014.[34]
Note: a small number of GT1a patients were enrolled in this study and have been excluded from the Genotype 1b efficacy population analyses but are included in the safety analyses.

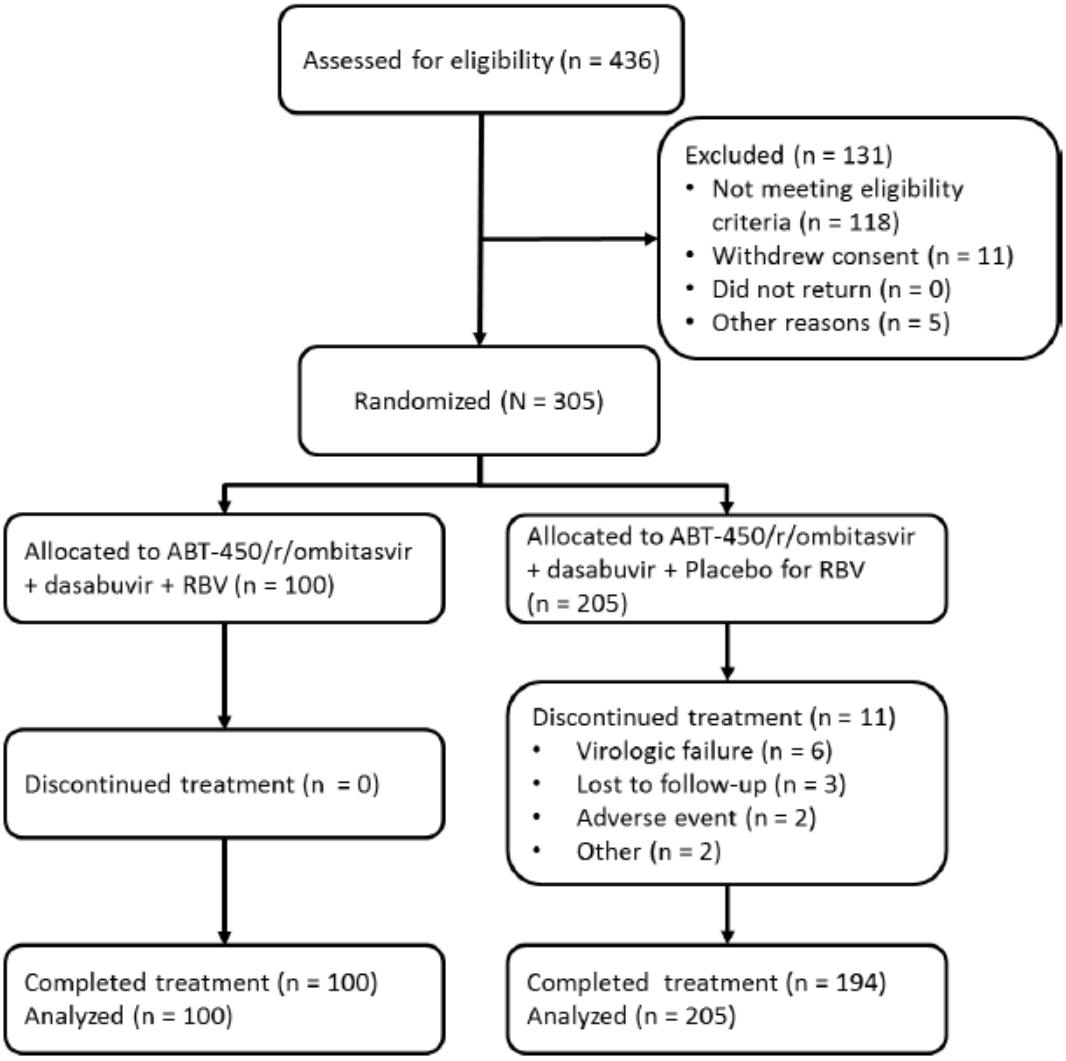
Figure 9: HCV GT1b - PEARL-III patient disposition



Source: Figure S2 Supplementary appendix of Ferenci *et al NEJM* 2014. [35]

Treatment naïve patients with chronic HCV genotype 1b infection were assessed for eligibility and randomised to receive either ABT450/r/ABT-267 and ABT-333 with ribavirin or placebo during the double blind period. Some patients reported multiple reasons for exclusion from the trial.

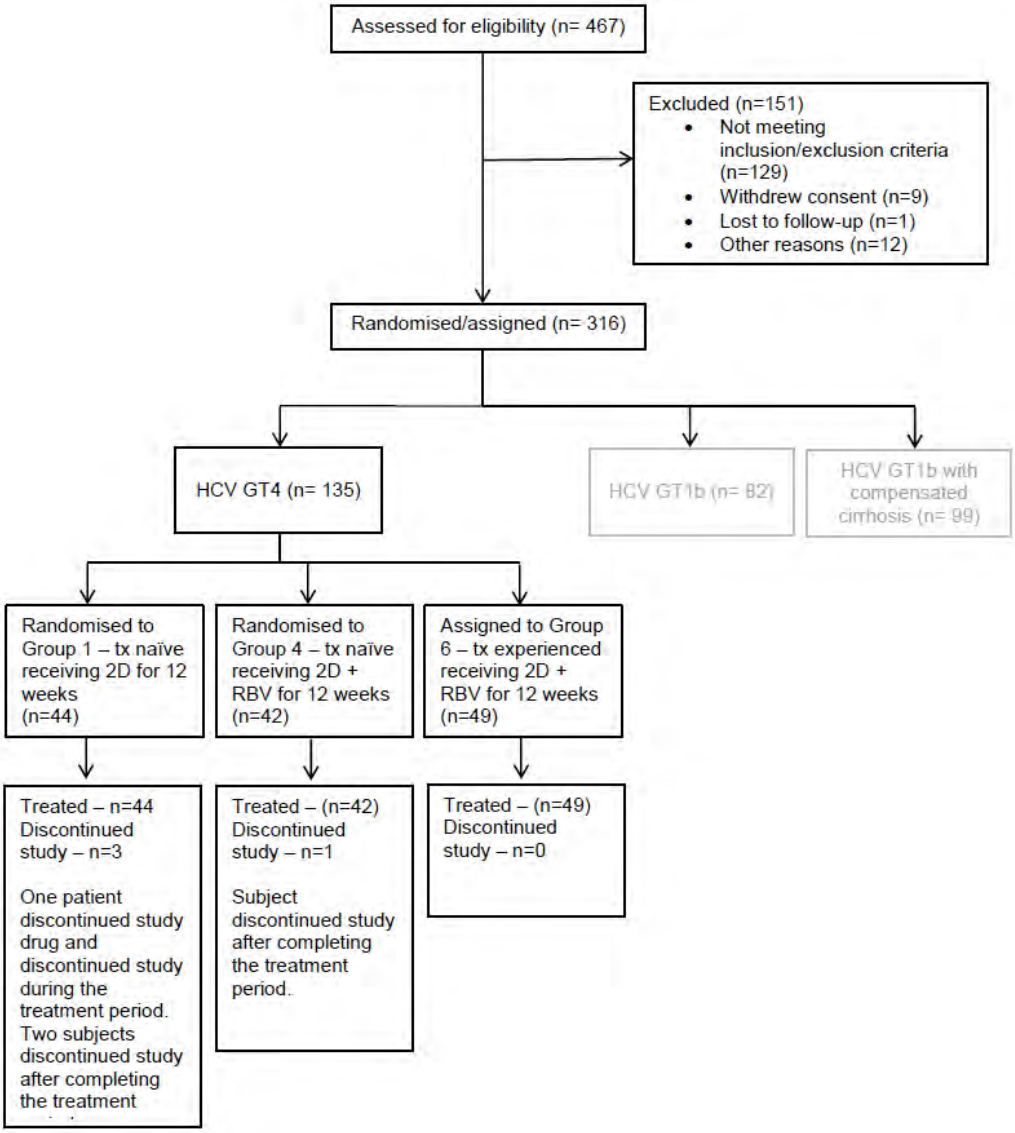
Figure 10: HCV GT1a - PEARL-IV patient disposition [35]



Source: Figure S1 Supplementary appendix of Ferenci *et al NEJM* 2014.[35]

Treatment naïve patients with chronic HCV genotype 1a infection were assessed for eligibility and randomised to receive either ABT450/r/ABT-267 and ABT-333 with ribavirin or placebo during the double blind period. Some patients reported multiple reasons for exclusion from the trial.

Figure 11: HCV GT4 – PEARL-I patient disposition [39]



Source: Adapted from CSR [39]

6.4 Critical appraisal of relevant RCTs

6.4.1 **The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies.**

6.4.2 **Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.**

Complete quality assessments of each phase III trial in AbbVie's HCV GT1 clinical trial programme and also the phase II trial in GT4 patients are presented in Appendix 10.3.

6.4.3 **If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.**

A summary of the critical appraisal for AbbVie's HCV clinical trial programme detailed in Appendix 10.3 is provided in Table 37 below.

Table 37 - Quality assessment results for RCTs

Trial no. (acronym)	SAPPHIRE-I	SAPPHIRE-II	TURQUOISE-II	PEARL-I	PEARL-II	PEARL-III	PEARL-IV
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	N/A	N/A	N/A	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	N/A	N/A	N/A	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	No	N/A	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

6.5 Results of the relevant RCTs

6.5.1 **Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given**

Sections 6.5.1.1 to 6.5.1.10 provide detailed results for all the clinical trials evaluating 3D +/- RBV in HCV GT1 patients. Section 6.5.1.11 provides detailed results evaluating 2D in HCV GT4 treatment naïve and treatment experienced patients.

6.5.1.1 Results from SAPPHIRE-I (M11-646) – treatment naïve HCV GT1 patients without cirrhosis

Primary outcome measure

Table 38 provides sustained virological response rates post-treatment week 12 (SVR12) for HCV genotype 1 treatment naïve subjects from the active arm of SAPPHIRE-I who were randomised to receive 3D + RBV for 12 weeks. As mentioned in Section 6.3, SVR12 data were not collected in the placebo-controlled arm; subjects receiving placebo for the first 12 weeks then received open-label 3D + RBV for a further 12 weeks.

As discussed in Section 6.3.6, 1 subject from SAPPHIRE-I was not available to have their 12 week post-treatment SVR status recorded prior to primary endpoint data lockdown. As such the CSR and publication in *NEJM* for this trial recorded this patient as a non-responder as per the SAP for missing data. However, at subsequent clinical visits following primary endpoint data lock-down, the SVR status was collected. As per the SAP and per the trial protocol, backward imputation of the SVR rate for this patient was possible. Therefore, the data presented in Table 38 differ slightly to the SVR rates reported in Feld *et al* and the CSR.

Table 38: SVR12 for HCV genotype 1 treatment naïve subjects from the active arm of SAPPHIRE-I (Group A) – 3D + RBV for 12 weeks[1]

Treatment outcome	3D + RBV for 12 weeks		
	n/N	%	95% CI
Overall SVR12	**456/473**	**96.4**	**94.7, 98.1**
HCV genotype 1a	308/322	95.7	93.4, 97.9
HCV genotype 1b	148/151	98.0	95.8, 100.0
Outcome for subjects without SVR12			
On-treatment virological failure [a]	1/473	0.2	
Relapse [b]	7/463	1.5	
Other [c]	9/473	1.9	

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

An additional point to note is that the data presented in Table 38 for genotype 1b are included because it was a pre-specified secondary outcome measure for this trial; however, the study arm evaluated 3D + RBV which is outside the licence for 3D in patients with genotype 1b. The SPC states that adults with HCV genotype 1b without cirrhosis should be given 3D as a monotherapy.

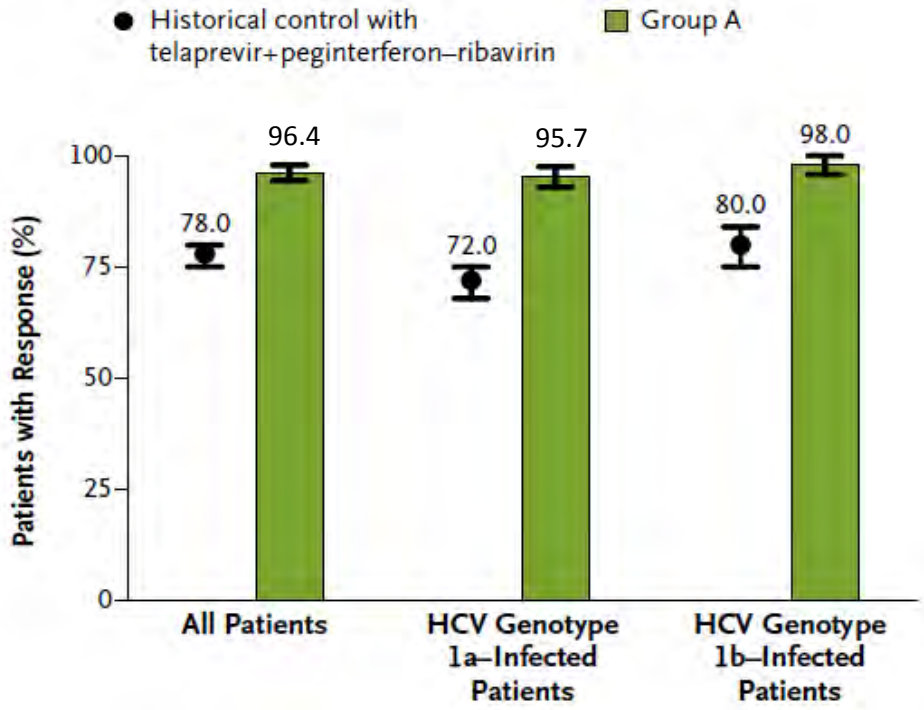
Secondary outcome measures

- SVR12 according to HCV sub-genotype (1a or 1b)

Table 38 presents SVR data according to sub-genotype.

Figure 12 below presents the SVR12 rates for the overall population and according to sub-genotype for 3D + RBV vs. historical telaprevir SVR rates. This figure clearly shows that 3D + RBV was superior to telaprevir in the overall population and by sub-genotype. Please see Table 26 for details of the statistical analysis to calculate non-inferiority and superiority of 3D vs. telaprevir.

Figure 12: SVR12 for the overall population and according to sub-genotype for 3D + RBV vs. historical telaprevir SVR rates



Adapted from Feld et al [31]

- Normalisation of the alanine aminotransferase level

Normalisation of the alanine aminotransferase level was defined as a final level that was no more than the upper limit of the normal range during the double-blind treatment period in patients whose baseline level had been higher than the upper limit of the normal range. The rate of normalisation of the alanine aminotransferase level was 97.0% in group A (352 of 363 patients), as compared with 14.9% in group B (17 of 114) (P<0.001).[31]

- Virologic failure during treatment

Patients were considered to have virologic failure during treatment if they had a confirmed HCV RNA level of 25 IU per millilitre or more after the HCV RNA level had been lower than 25 IU per millilitre during treatment, if they had a confirmed increase in the HCV RNA level of more than 1 log10 IU per millilitre above the nadir observed during treatment, or if all the HCV RNA values during the treatment with the study drug administered for at least 6 weeks were 25 IU per millilitre or more. [31]

Among the 473 patients in the arm receiving 3D + RBV, 1 patient (0.2%) had virologic failure during the double-blind treatment period. In this HCV genotype 1a–infected patient who had adhered to the treatment regimen, the HCV RNA level became quantifiable at treatment week 12. [31]

- Post-treatment relapse

Virologic relapse was defined as a confirmed HCV RNA level of 25 IU per millilitre or more between the final treatment visit and 12 weeks after receipt of the last dose of study drug among patients who completed treatment (duration of treatment, ≥77 days), who had an HCV RNA level that was lower than 25 IU per millilitre at the final treatment visit during the double-blind period, and who had HCV RNA data available after treatment. [31]

A total of 7 of 463 patients (1.5%) had a relapse by post-treatment week 12, of whom 5 had a relapse at or before the visit at post-treatment week 4. [31]

Each of the eight patients who had virologic failure - during treatment (n=1) or relapse (n=7) - had at least one amino acid variant that was known to confer resistance to one of the three direct-acting antiviral agents included in the regimen. The most frequently detected variants in the seven patients with HCV genotype 1a infection at the time of virologic failure during treatment or relapse were D168V (in six patients) in the protein NS3, M28T (in two) and Q30R (in three) in the protein NS5A, and S556G (in three) in the protein NS5B. The single patient with HCV genotype 1b infection who had relapse had variants Y56H and D168V in the protein NS3, L31M and Y93H in the protein NS5A, and S556G in the protein NS5B at the time of relapse. [31]

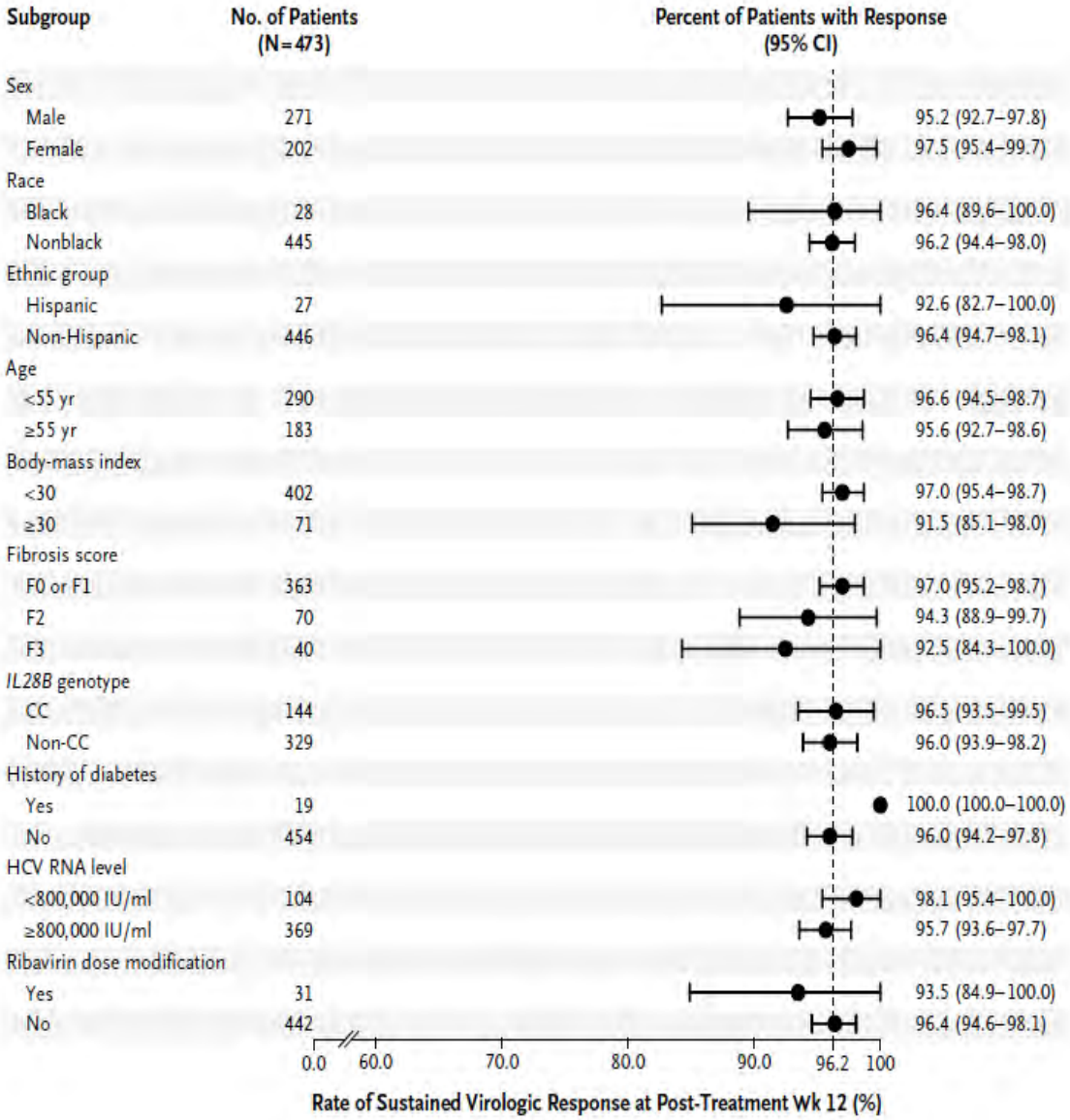
<u>Sub-group analyses of SVR12 rates</u>

Figure 13 shows the rates of SVR12 stratified by sub-groups and other baseline characteristics. The rates were similarly high in all sub-groups, including those defined by IL28B genotype (96.5% with CC and 96.0% with non-CC), race (96.4% among black patients and 96.2% among non-black patients), fibrosis score at baseline (97.0% with a score of F0 or F1, 94.3% with a score of F2, and 92.5% with a score of F3), and baseline HCV RNA level (98.1% with a level <800,000 IU per

millilitre and 95.7% with a level ≥800,000 IU per millilitre). The rate of sustained virologic response at post-treatment week 12 was 93.5% among patients who had a modification of the ribavirin dose (29 of 31 patients) and 96.4% among those who did not have a dose modification (426 of 442). [31]

Stepwise logistic-regression analysis showed that characteristics such as age, sex, race, ethnic group, IL28B genotype, fibrosis score, and baseline viral load did not have a significant effect on the sustained virologic response at post-treatment week 12. Only high baseline BMI was associated with a reduced rate, although the effect was modest (odds ratio, 0.89; P = 0.02); even among patients with a body-mass index of 30 or more, the rate of sustained virologic response at post-treatment week 12 was high (91.5%). [31]

Figure 13: SVR12 from SAPPHIRE-I by patient characteristics



Source: Feld et al [31]. Note this figure does not include the additional GT1a patient who achieved SVR12 after primary endpoint data lockdown.

<u>Exploratory outcome measures - HRQoL</u>

Table 39 presents a comparison between treatment groups (3D vs. placebo) for the mean change from baseline to the final clinical visit of the double-blind treatment period. [redacted] [42]

Please note that the EQ-5D-5L health index scores have been derived using where possible country specific algorithms to cross-walk the 5L values to the 3L tariff scores, as country specific tariffs for the EQ-5D-5L are currently in development. Where an individual country does not have a crosswalk, the US crosswalk to convert the 5L values to 3L has been used. Therefore, the mean health index values for the EQ-5D-5L presented in Table 39 below have been calculated using a number of different countries algorithms, which make the data difficult to interpret. For the economic modelling, see Section 7.4, the UK cross-walk has been applied to the entire data set to ensure consistency in the methodology of obtaining utility values, and thus any differences can be attributed to an actual change in HRQoL rather than sampling of country-specific tariff differences.

Table 39: Comparison of the mean change from baseline to the final double-blind treatment period visit and the final post-treatment visit in PRO scores for 3D + RBV vs. placebo – SAPPHIRE-I

Instrument	3D + RBV			Placebo		
	N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
SF-36 PCS						
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
SF-36 MCS						
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
EQ-5D-5L visual analogue score						
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
EQ-5D-5L health index score						
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		

HCV-PRO total score						
Final double-blind treatment period visit*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		

* Statistically significant difference between treatment groups at *P* = 0.05 level.

Treatment compliance

In SAPPHIRE-I, patients in the active treatment arm took an average of 98.9% or more of their prescribed doses of each pill (including RBV). [31]

6.5.1.2 Results from SAPPHIRE-II (M13-098) – PegIFN/RBV treatment experienced HCV GT1 patients without cirrhosis

Primary outcome measure

Table 40 provides SVR12 rates for HCV GT1 treatment-experienced subjects from the active arm of SAPPHIRE-II who were randomised to receive 3D + RBV for 12 weeks. As mentioned in Section 6.3, SVR12 data were not collected in the placebo-controlled arm; subjects receiving placebo for the first 12 weeks then received open-label 3D + RBV for a further 12 weeks. A total of 286 patients in the active-regimen group had SVR at post-treatment week 12, for an overall rate of 96.3% (95% CI, 94.2 to 98.4); this was non-inferior and superior to the historical control rate with telaprevir and PegIFN/RBV in treatment-experienced patients. For more information on the statistical analysis performed to calculate non-inferiority and superiority see Table 7.

Table 40: SVR12 for HCV genotype 1 PegIFN/RBV treatment-experienced subjects from the active arm of SAPPHIRE-II receiving 3D + RBV for 12 weeks [32]

Treatment outcome	3D + RBV for 12 weeks		
	n/N	%	95% CI
Overall SVR12	286/297	96.3	94.1, 98.4
HCV genotype 1a	166/173	96.0	93.0, 98.9
Prior PegIFN/RBV null responder	83/87	95.4	91.0, 99.8
Prior PegIFN/RBV partial responder	36/36	100	100.0, 100.0
Prior PegIFN/RBV relapser	47/50	94.0	87.4, 100.0
HCV genotype 1b	119/123	96.7	93.6, 99.9
Prior PegIFN/RBV null responder	56/59	94.9	89.3, 100.0
Prior PegIFN/RBV partial responder	28/28	100	100.0, 100.0
Prior PegIFN/RBV relapser	35/36	97.2	91.9, 100.0
Outcome for subjects without SVR12			
On-treatment virological failure [a]	0/297	0	
Relapse [b]	7/293	2.4	
Other [c]	4/297	1.3	

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Secondary outcome measures

- Normalisation of the alanine aminotransferase level

Normalisation of the alanine aminotransferase level was defined as a final level that was no more than the upper limit of the normal range during the double-blind treatment period in patients whose baseline level had been higher than the upper limit of the normal range. The rate of normalisation of the alanine aminotransferase level was significantly higher in the active-regimen group than in the placebo group (96.9% [217 of 224 patients] vs. 12.8% [10 of 78 patients], P<0.001). [32]

- Virologic failure during treatment

No patient had virologic failure during treatment; all patients completing treatment (≥77 days of study-drug exposure) had an HCV RNA level of less than 25 IU per millilitre at the end of treatment. [32]

- Post-treatment relapse

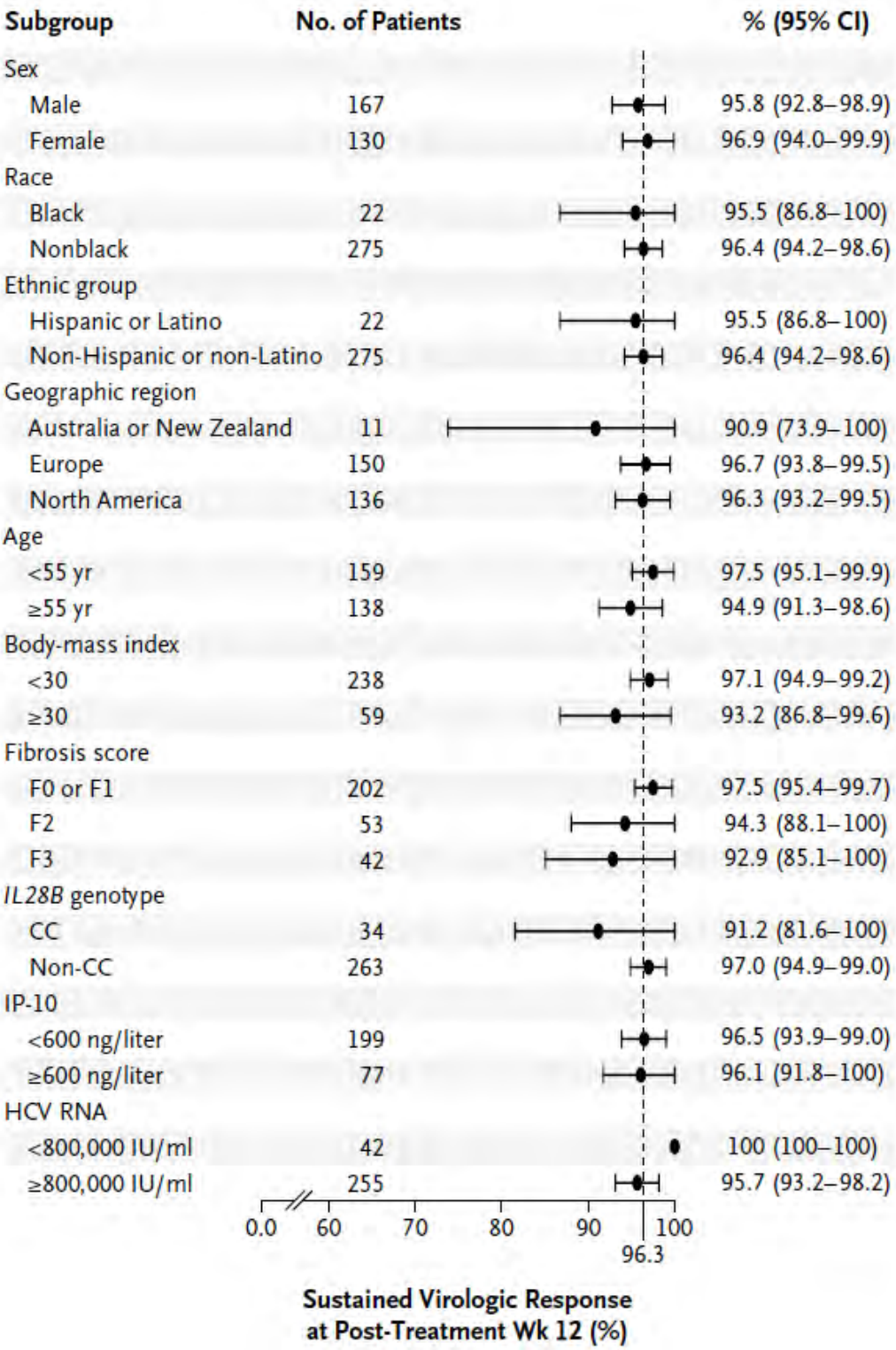
Seven of 293 patients who completed therapy (2.4%) had post-treatment viral relapse. All patients with relapse reported high adherence to study drugs. At the time of relapse, 4 of the 5 patients with HCV genotype 1a infection and 1 of the 2 patients with HCV genotype 1b infection had at least one amino acid variant known to confer resistance to one of the three direct-acting antiviral agents included in the regimen. The most frequently detected variants in the 4 patients with HCV genotype 1a infection who had variants at the time of relapse were D168V in NS3 (2 patients), M28V (3 patients) and Q30R (2 patients) in NS5A, and S556G in NS5B (2 patients). The patient with HCV GT1b who had resistance associated variants present at the time of relapse had Y56H and D168A in NS3, Y93H in NS5A, and C316N and S556G in NS5B. [32]

Sub-group analyses of SVR12 rates

There were a number of pre-specified SVR12 sub-group analyses in the trial protocol. Table 40 presents SVR12 rates and 2-sided CIs by HCV GT1 sub-genotype and also by type of response to previous PegIFN/RBV treatment.

Figure 14 below presents SVR12 data for the rest of the pre-specified sub-groups stipulated in the trial protocol. Rates of sustained virologic response were high across subgroups defined by race, age, fibrosis score, and *IL28B* genotype. [32]

Figure 14: SVR12 according to pre-specified sub-groups for subjects receiving 12 weeks of 3D + RBV in SAPPHIRE-II



Source: Zeuzem *et al.* [32]

Exploratory outcome measures [43]

Table 41 presents a comparison between treatment groups (3D vs. placebo) for the mean change in PRO scores from baseline to the final clinical visit of the double-blind treatment period and also the final post-treatment visit. [redacted] [43]

As mentioned in 6.5.1.1, the EQ-5D-5L health index scores have been derived using country specific algorithms to cross-walk the 5L values to the 3L tariff scores. Where an individual country does not have a crosswalk, the US crosswalk to convert the 5L values to 3L has been used. Therefore, the mean health index values for the EQ-5D-5L presented in Table 41 below have been calculated using a number of different countries algorithms, which make the data difficult to interpret. For the economic modelling, see Section 7.4, the UK cross-walk has been applied to the entire data set to ensure consistency in the methodology of obtaining utility values, and thus any differences can be attributed to an actual change in HRQoL rather than sampling of country-specific tariff differences. [43]

Table 41: Comparison of the mean change from baseline to the final double-blind treatment period visit and the final post-treatment visit in PRO scores for 3D + RBV vs. placebo – SAPPHIRE-II

Instrument	3D + RBV			Placebo		
	N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
SF-36 PCS						
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
SF-36 MCS						
Final double-blind treatment period visit*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
EQ-5D-5L visual analogue score						
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
EQ-5D-5L health index score						
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
HCV-PRO total score						
Final double-blind treatment period visit*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		

* Statistically significant difference between treatment groups at *P* = 0.05 level.

Treatment compliance [43]

In SAPPHIRE-II, patients in the active treatment arm took an average of 99.46% or more of their prescribed doses of each pill (including RBV).

6.5.1.3 Results from TURQUOISE-II (M13-099) – treatment naïve and PegIFN/RBV treatment experienced HCV GT1 patients with compensated cirrhosis

Primary outcome measure

Table 42 provides SVR12 rates for HCV genotype 1-infected subjects with compensated cirrhosis who were treatment naïve or previously treated with PegIFN/RBV, randomised to receive either 3D + RBV for 12 weeks or 3D + RBV for 24 weeks in TURQUOISE-II.

As discussed in Section 6.3.6, 1 subject from TURQUOISE-II was not available to have their 12 week post-treatment SVR status recorded prior to primary endpoint data lockdown. As such the CSR and publication in NEJM for this trial recorded this patient as a non-responder as per the SAP for missing data. However, at subsequent clinical visits following primary endpoint data lock-down, the SVR status was collected. As per the SAP and per the trial protocol, backward imputation of the SVR rate for this patient was possible. Therefore, the data presented in Table 42 differ slightly to the SVR rates reported in Poordad *et al* and the CSR. [1, 33]

A total of 191 of 208 patients who received 3D + RBV for 12 weeks achieved SVR12 - 91.8% (97.5% CI, 87.6 to 96.1). A total of 166 of 172 patients who received 3D for 24 weeks had SVR12, 96.5% (97.5% CI, 93.4 to 99.6). In both treatment groups, the primary efficacy end points met the pre-specified criteria for non-inferiority and superiority to the historical rate with telaprevir plus PegIFN/RBV among patients with HCV GT and cirrhosis. Rates of sustained virologic response in subgroups defined by HCV sub-genotype, status with respect to prior treatment, and type of treatment failure among previously treated patients were also superior to the historical rate.

Table 42: SVR12 for genotype 1-infected subjects with compensated cirrhosis who were treatment-naïve or previously treated with PegIFN/RBV from TURQUOISE-II [1, 33]

Treatment outcome	3D + RBV for 12 weeks			3D + RBV for 24 weeks		
	n/N	%	CI[a]	n/N	%	CI[a]
Overall SVR12	**191/208**	**91.8%**	**87.6, 96.1**	**166/172**	**96.5**	**93.4, 99.6**
HCV genotype 1a	**124/140**	**88.6**	**83.3, 93.8**	**115/121**	**95.0**	**91.2, 98.9**
Treatment naïve	59/64	92.2	-	53/56	94.6	-
Prior PegIFN/RBV null responder	40/50	80.0	-	39/42	92.9	-
Prior PegIFN/RBV partial responder	11/11	100	-	10/10	100	-
Prior PegIFN/RBV relapser	14/15	93.3	-	13/13	100	-
HCV genotype 1b	**67/68**	**98.5**	**95.7, 100.0**	**51/51**	**100**	**100.0, 100.0**
Treatment naïve	22/22	100	-	18/18	100	-
Prior PegIFN/RBV null responder	25/25	100	-	20/20	100	-
Prior PegIFN/RBV partial responder	6/7	85.7	-	3/3	100	-
Prior PegIFN/RBV relapser	14/14	100	-	10/10	100	-
Outcome for subjects without SVR12						
On-treatment virological failure [b]	1/208	0.5		3/172	1.7	
Relapse [c]	12/203	5.9		1/164	0.6	
Other [d]	4/208	1.9		2/172	1.21	

a. 97.5% confidence intervals are used for the primary efficacy endpoints (overall SVR12 rate); 95% confidence intervals are used for additional efficacy endpoints (SVR12 rates in HCV genotype 1a and 1b-infected subjects).

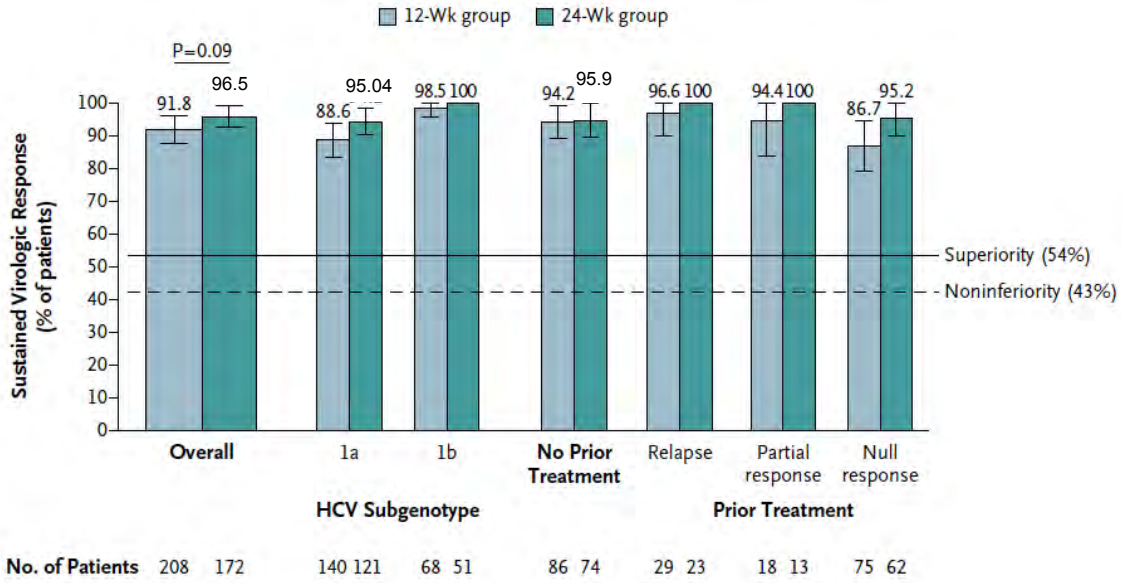
b. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

c. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 or 22 weeks of treatment, for subjects assigned to 12 or 24 weeks of treatment, respectively.

d. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Figure 15 below shows SVR12 in each treatment group, overall and according to sub-groups compared to the historical telaprevir SVR rate; SVR rates both overall and according to sub-group, are superior to the historical SVR rates for telaprevir + PegIFN/RBV in HCV GT1 patients with compensated cirrhosis.

Figure 15: SVR12 in each treatment group, overall and according to sub-groups compared to the historical telaprevir SVR rate



Adapted from Poordad *et al.*[33]

Secondary outcome measures

The key secondary efficacy endpoint looking at the percentage of patients with SVR12 in the 24 week group as compared with the 12-week group is presented in Table 42. The difference in the rates of sustained virologic response between the two treatment groups was not significant (P = 0.09). Rates were also similar in the two treatment groups across the randomisation strata. Additional pre-specified secondary outcome measures are presented below.

- Virologic failure during treatment

Virologic failure during treatment occurred in 1 of 208 patients in the 12-week group (0.5% [95% CI, 0 to 1.4]) and in 3 of 172 patients in the 24-week group (1.7% [95% CI, 0 to 3.7]). [33]

- Post-treatment relapse

Significantly more patients in the 12-week group than in the 24-week group had a relapse: 12 of 203 patients, for a rate of 5.9% (95% CI, 2.7 to 9.2), versus 1 of 164 patients, for a rate of 0.6% (95% CI, 0 to 1.8). Seven of the 12 patients with a relapse in the 12-week group (58.3%) had HCV genotype 1a infection and a prior null response to PegIFN/RBV treatment. [33]

Virologic resistance was assessed by means of population sequencing of samples from the 17 patients who had virologic failure (either during treatment or post-treatment relapse). At the time of virologic failure, 2 patients had no resistance-associated variants detected in NS3, NS5A, or NS5B. The remaining 15 patients had

resistance-associated variants in two or more of the drug targets, with variants D168V (NS3) and Q30R (NS5A) observed most frequently in patients with HCV genotype 1a infection and D168V (NS3), Y93H (NS5A), and C316Y and M414I (NS5B) observed in the single patient with HCV genotype 1b infection. [33]

Sub-group analyses of SVR12

Table 43 presents the SVR12 rates according to pre-specified sub-groups. As can be seen from the table, rates did not differ substantially according to race, body-mass index, *IL28B* genotype, status with respect to a history of diabetes mellitus, status with respect to a history of depression or bipolar disorder, or baseline HCV RNA level. [33] Note this sub-group analysis does not include the additional patient who achieved SVR12 after primary endpoint data lockdown.

Table 43: SVR12 rates according to pre-specified patient sub-groups from subjects with HCV GT1 from TURQUOISE-II

	12 Weeks of 3D +RBV (N=208)	24 weeks of 3D + RBV (N=172)
Variable	**Number with SVR12/total number percent (95%CI)**	
Sex		
Male	133/146 91.1 (86.5, 95.7)	116/121 95.9 (92.3, 99.4)
Female	58/62 93.5 (87.4, 99.7)	49/51 96.1 (90.8, 100.0)
Age		
<55 years	53/58 91.4 (84.2, 98.6)	56/60 93.3 (87.0, 99.6)
≥ 55 years	138/150 92.0 (87.7, 96.3)	109/112 97.3 (94.3, 100.0)
Race		
Black	6/6 100.0 (N/A)	5/6 83.3 (N/A)
Non-black	185/202 91.6 (87.8, 95.4)	160/166 96.4 (93.5, 99.2)
Ethnicity		
Hispanic or Latino	21/25 84.0 (69.6, 98.4)	19/20 95.0 (85.4, 100.0)
Not Hispanic or Latino	170/183 92.9 (89.2, 96.6)	146/152 96.1 (93.0, 99.1)
Baseline BMI		
< 30 kg/m^2	135/146 92.5 (88.2, 96.7)	122/126 96.8 (93.8, 99.9)
≥ 30 kg/m^2	56/62 90.3 (83.0, 97.7)	43/46 93.5 (86.3, 100.0)
History of diabetes		
Yes	25/29 86.2 (73.7, 98.8)	30/31 96.8 (90.6, 100.0)
No	166/179 92.7 (88.9, 96.5)	135/141 95.7 (92.4, 99.1)
History of depression or bipolar disorder		

Yes	48/51 94.1 (87.7, 100.0)	41/43 95.3 (89.1, 100.0)
No	143/157 91.1 (86.6, 95.5)	124/129 96.1 (92.8, 99.5)
Baseline child-Pugh score		
5	158/170 92.9 (89.1, 96.8)	136/140 97.1 (94.4, 99.9)
6	33/38 86.8 (76.1, 97.6)	24/27 88.9 (77.0, 100.0)
>6	0	5/5 100.0 (N/A)
Baseline platelet count		
<90x109/L	25/30 83.3 (70.0, 96.7)	25/26 96.2 (88.8, 100.0)
≥90x109/L	166/178 93.3 (89.6, 96.9)	140/146 95.9 (92.7, 99.1)
Baseline albumin		
< 35 g/L	21/25 84.0 (69.6, 98.4)	16/18 88.9 (74.4, 100.0)
≥ 35 g/L	170/183 92.9 (89.2, 96.6)	149/154 96.8 (94.0, 99.6)
Baseline alpha fetoprotein		
< 20 ng/mL	145/152 95.4 (92.1, 98.7)	117/121 96.7 (93.5, 99.9)
≥ 20 ng/mL	46/56 82.1 (72.1, 92.2)	48/51 94.1 (87.7, 100.0)
Baseline HCV RNA		
< 800,000 IU/mL	31/34 91.2 (81.6, 100.0)	17/19 89.5 (75.7, 100.0)
≥ 800,000 IU/mL	160/174 92.0 (87.9, 96.0)	148/153 96.7 (93.9, 99.5)
IL28 genotype		
CC	33/35 94.3 (86.6, 100.0)	33/34 97.1 (91.4, 100.0)
Non-CC	158/173 91.3 (87.1, 95.5)	132/138 95.7 (92.2, 99.1)
Ribavirin dose modification		
Yes	18/18 100.0 (100.0, 100.0)	25/25 100.0 (100.0, 100.0)
No	173/190 91.1 (87.0, 95.1)	140/147 95.2 (91.8, 98.7)

Source: Supplementary appendix from Poordad et al [33]

Exploratory outcomes

Table 44 presents a comparison between treatment groups (12 week vs 24 weeks treatment with 3D + RBV) for the mean change in PRO score from baseline to the final treatment period visit and also the post-treatment week 12 visit. [redacted] [44]

Table 44: Mean change in PRO scores from baseline to the final treatment period visit and also the post-treatment week 12 visit – TURQUOISE-II

Instrument	3D + RBV for 12 weeks			3D + RBV for 24 weeks		
	N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
SF-36 PCS						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 MCS						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L visual analogue score						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L health index score						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HCV-PRO total score						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As previously mentioned, the EQ-5D-5L health index scores have been derived using country specific algorithms to cross-walk the 5L values to the 3L tariff scores. Where an individual country does not have a crosswalk, the US crosswalk to convert the 5L values to 3L has been used. Therefore, the mean health index values for the EQ-5D-5L presented in the table above have been calculated using a number of different countries algorithms, which make the data difficult to interpret.

Treatment compliance

In TURQUOISE-II, patients took on average at least 98.65% or more of their prescribed doses of each pill (including RBV).[44]

6.5.1.4 Results from PEARL-II (M13-389) – PegIFN/RBV treatment experienced HCV GT1b patients without cirrhosis

Primary outcome measure

Table 45 provides SVR12 rates for HCV genotype 1b-infected subjects who were previously treated with PegIFN/RBV and received open-label 3D with RBV or 3D without RBV for 12 weeks in PEARL-II. For the primary end point, SVR12 rates in both treatment groups were non-inferior to the historical SVR rate for telaprevir plus PegIFN/RBV in comparable treatment-experienced patients. Both treatment groups

also were superior to the historical rate. See Table 28 for details of the statistical analyses used to determine the superiority and non-inferiority calculations.

As discussed in Section 6.3.6, 1 subject from PEARL-II was not available to have their 12 week post-treatment SVR status recorded prior to primary endpoint data lockdown. As such the CSR and publication in Gastroenterology for this trial recorded this patient as a non-responder as per the SAP for missing data. However, at subsequent clinical visits following primary endpoint data lock-down, the SVR status was collected. As per the SAP and per the trial protocol, backward imputation of the SVR rate for this patient was possible. Therefore, the data presented in Table 45 differ slightly to the SVR rates reported in Andreone *et al* and the CSR.

Table 45: SVR12 for HCV GT1b PegIFN/RBV treatment-experienced subjects in PEARL-II [1, 34]

Treatment outcome	3D + RBV for 12 weeks			3D for 12 weeks		
	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	86/88	97.7	94.6, 100.0	91/91	100	95.9, 100.0
Prior PegIFN/RBV null responder	30/31	96.8	90.6, 100.0	32/32	100	89.3, 100.0
Prior PegIFN/RBV partial responder	24/25	96.0	88.3, 100.0	26/26	100	87.1, 100.0
Prior PegIFN/RBV relapser	32/32	100	89.3, 100.0	33/33	100	89.6, 100.0
Outcome for subjects without SVR12						
On-treatment virological failure [a]	0/88	0		0/91	0	
Relapse [b]	0/88	0		0/91	0	
Other [c]	2/88	2.3		0/91	0	

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Secondary outcome measures

Non-inferiority of 3D without ribavirin to the group administered 3D with ribavirin was clearly shown given that the 3D monotherapy group achieved higher SVR rates than the 3D + RBV group (100% vs. 97.1%).[1]

- Virological failure during treatment and post-treatment relapse

No patients from either treatment group experienced on-treatment virologic failure or post-treatment relapse. The 2 (2.3%) patients in the 3D + RBV group who did not achieve SVR12 discontinued study drug because of AEs.[34]

- Percentage of subjects with a decrease in haemoglobin to below the lower limit of normal (LLN) at the end of treatment

Haemoglobin levels less than the lower limit of normal at the end of treatment was experienced more often by patients in group 1 (3D + RBV) compared with patients in group 2 (3D) (42.0% vs 5.5%, respectively; P < .001), although clinically significant grade 2 haemoglobin level declines to less than 10 g/dL at the end of treatment occurred in only 2 (1.1%) patients, both in group 1. No patient required a blood transfusion or erythropoietin. [34]

Sub-group analyses of SVR12

Sustained virologic responses in both groups were not influenced by previous non-response, age, race, or interleukin 28B genotype. Among group 1 null responders, partial responders, and relapsers to previous PegIFN/RBV treatment, SVR12 rates were 96.8%, 96.0%, and 100%, respectively. Group 1 rates were similarly high regardless of interleukin 28B genotype (CC, 100%; CT, 96.4%; and TT, 95.5%), or sex (male, 95.3%; female, 97.8%). Group 2 SVR12 rates were 100% in all subgroups. Note this analysis does not include the patient that had SVR data available after the post-treatment week 12 visit. [34]

Finally, the 7 patients excluded from the efficacy subset because they received non-coformulated study drug, had confirmed genotype 1a, or undetermined genotype, all completed treatment and achieved SVR12. [34]

Exploratory outcomes – HRQoL[45]

A comparison between treatment groups for the mean change from baseline to the final treatment period visit and final post-treatment period visit in PRO scores is presented in Table 46. [redacted] [45]

Table 46: Mean change in PRO scores from baseline to the final treatment period visit and also the post-treatment week 12 visit – PEARL-II

Instrument	3D + RBV for 12 weeks			3D for 12 weeks		
	N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
SF-36 PCS						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 MCS						
Final treatment visit *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L visual analogue score						
Final treatment visit *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L health index score						
Final treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

visit						
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HCV-PRO total score						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Statistically significant difference between treatment groups at $P \leq 0.05$ level.[45]

As previously mentioned, the EQ-5D-5L health index scores have been derived using country specific algorithms to cross-walk the 5L values to the 3L tariff scores. Where an individual country does not have a crosswalk, the US crosswalk to convert the 5L values to 3L has been used. Therefore, the mean health index values for the EQ-5D-5L presented in the table above have been calculated using a number of different countries algorithms, which make the data difficult to interpret.

Treatment compliance

In PEARL-II, patients took on average at least 99.10% or more of their prescribed doses of each pill (including RBV).[45]

6.5.1.5 Results from PEARL-III (M13-961) – treatment naïve HCV GT1b patients without cirrhosis

Primary outcome measure

Table 47 provides SVR12 rates for HCV GT1b treatment-naive subjects from PEARL-III who were randomised to receive either 3D + RBV or 3D for 12 weeks. The table shows that 99.5% and 100% of patients receiving 3D +RBV and 3D alone achieved SVR 12, respectively.[1] Thus, SVR rates among patients who received ribavirin and those who did not were both non-inferior and superior to the historical rate with telaprevir plus PegIFN/RBV among previously untreated adults with HCV genotype 1b infection and no cirrhosis.[35]

Table 47: SVR12 for HCV GT1b treatment-naive subjects from PEARL-III [1, 35]

Treatment outcome	3D + RBV for 12 weeks			3D for 12 weeks		
	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	209/210	99.5	98.6, 100.0	209/209	100.0	98.2,100.0
Outcome for subjects without SVR12						
On-treatment virological failure [a]	1/210	0.5		0/209	0	
Relapse [b]	0/210	0		0/209	0	
Other [c]	0/210	0		0/209	0	

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Please note 2 subjects from PEARL-III were not available to have their 12 week post-treatment SVR status recorded prior to primary endpoint data lockdown. As such the CSR and publication in *NEJM* for this trial recorded this patient as a non-responder as per the SAP for missing data. However, at subsequent clinical visits following primary endpoint data lock-down, the SVR status was collected. As per the SAP and per the trial protocol, backward imputation of the SVR rate for this patient was possible. Therefore, the data presented in Table 47 differ slightly to the SVR rates reported in Ferenci *et al* and the CSR.

Secondary outcome measures

- Non-inferiority in SVR12 rates for 12 weeks of 3D without RBV to 12 weeks treatment of 3D with RBV

The sustained-virologic-response rate among patients who did not receive ribavirin was non-inferior to the rate among those who received ribavirin (difference, −0.5 percentage points [95% CI, −2.1 to 1.1]). [35]

- Virological failure during treatment

Only one patient with genotype 1b infection had virologic failure during treatment; this patient, who received the antiviral regimen with ribavirin, had a virologic rebound during treatment. [35]

- Post-treatment relapse

No patients experienced post-treatment relapse in either arm of PEARL-III. [35]

- Percentage of subjects with a decrease in haemoglobin to below the lower limit of normal (LLN) at the end of treatment

Among the patients in the genotype 1b study, 51.2% of patients who received ribavirin had a low haemoglobin level at the end of treatment, as compared with 3.4% of patients who did not receive ribavirin (P<0.001). A haemoglobin level of less than 10 g per decilitre at any time during treatment occurred in 9.0% of patients with genotype 1b infection who received ribavirin but did not occur in any patients who received the ribavirin-free regimen. The ribavirin dose was reduced in accordance with the protocol because of a decreased haemoglobin level in 16 patients with genotype 1b infection who received ribavirin (7.6%); all these patients had a sustained virologic response. [35]

Sub-group analyses of SVR12

Sub-group analyses of SVR12 according to patient characteristics showed that there were no significant predictors of response as SVR rates were high across all the different characteristics.

Exploratory outcome measures – HRQoL [46]

A comparison between treatment groups for the mean change from baseline to the final treatment period visit and final post-treatment period visit in PRO scores is presented in Table 48. [redacted] [46]

Table 48: Mean change in PRO scores from baseline to the final treatment period visit and also the post-treatment week 12 visit – PEARL-III

Instrument	3D + RBV for 12 weeks			3D for 12 weeks		
	N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
SF-36 PCS						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 MCS						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L visual analogue score						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L health index score						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HCV-PRO total score						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As previously mentioned, the EQ-5D-5L health index scores have been derived using country specific algorithms to cross-walk the 5L values to the 3L tariff scores. Where an individual country does not have a crosswalk, the US crosswalk to convert the 5L values to 3L has been used. Therefore, the mean health index values for the EQ-5D-5L presented in the table above have been calculated using a number of different countries algorithms, which make the data difficult to interpret.

Treatment compliance

In PEARL-III, patients took on average at least 99.57% or more of their prescribed doses of each pill (including RBV). [46]

6.5.1.6 Results from PEARL-IV (M14-002) – treatment naïve HCV GT1a patients without cirrhosis

Primary outcome measure

Table 49 provides SVR12 rates for HCV GT1a treatment-naive subjects from PEARL-IV who were randomised to receive either 3D + RBV or 3D for 12 weeks. The table shows that 97.0% and 90.2% of patients receiving 3D +RBV and 3D alone achieved SVR 12, respectively. Thus, SVR rates among patients who received ribavirin and those who did not were both non-inferior and superior to the historical rate with telaprevir plus PegIFN/RBV among previously untreated adults with HCV genotype 1a infection and no cirrhosis.[35]

Table 49: SVR12 for HCV GT1a treatment-naive subjects from PEARL-IV

Treatment outcome	3D + RBV for 12 weeks			3D for 12 weeks		
	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	97/100	97.0	93.7, 100.0	185/205	90.2	86.2, 94.3
Outcome for subjects without SVR12						
On-treatment virological failure [a]	1/100	1.0		6/205	2.9	
Relapse [b]	1/98	1.0		10/194	5.2	
Other [c]	1/100	1.0		4/205	2.0	

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Secondary outcome measures

- Non-inferiority in SVR12 rates for 12 weeks of 3D without RBV to 12 weeks treatment of 3D with RBV

The regimen without ribavirin did not meet the non-inferiority criterion compared to 3D with ribavirin, because the lower boundary of the confidence interval for the difference (−6.8 percentage points [95% CI, −12.0 to −1.5]) crossed the non-inferiority margin of 10.5 percentage points. In addition, the upper boundary of the confidence interval did not cross zero, indicating a significant difference between groups. [35]

- Virological failure during treatment and post-treatment relapse

A total of 18 patients with genotype 1a infection had virologic failure, 16 of whom received the regimen without ribavirin. Of the 3 patients with genotype 1a infection who received the regimen with ribavirin and did not have a SVR12, 2 had virologic failure (1 had a rebound in HCV RNA levels during treatment and 1 had a relapse after treatment), and 1 did not complete follow-up testing at post-treatment week 12. [35]

Of the 16 patients with genotype 1a infection who received the regimen without ribavirin and had virologic failure, 6 had a virologic rebound during treatment and 10 had a relapse after treatment. All the patients with a relapse received at least 11 weeks of treatment. Adherence to the dosing regimen for each study drug was greater than 95% for 16 of the 17 patients with virologic failure for whom data were available; 1 patient who received the antiviral regimen without ribavirin and had a

virologic rebound took 88.5% of the planned ABT-450/r–ombitasvir doses and 90.8% of the planned dasabuvir doses. [35]

At the time of virologic failure, each of the 18 patients with genotype 1a infection and a virologic failure had at least one resistance-associated variant known to be selected by one of the three direct-acting antiviral agents included in the regimen. The most frequently detected variants in patients with virologic failure were D168V in NS3, M28T and Q30R in NS5A, and S556G in NS5B. [35]

- Percentage of subjects with a decrease in haemoglobin to below the lower limit of normal (LLN) at the end of treatment

Among the patients in the genotype 1a study who had a haemoglobin level within the normal range at baseline, 42.0% of patients who received the antiviral regimen with ribavirin and 3.9% of patients who received the ribavirin-free regimen had a haemoglobin level below the lower limit of the normal range at the end of treatment (P<0.001). A haemoglobin level of less than 10 g per decilitre at any time during treatment occurred in 4.0% of patients with genotype 1a infection who received ribavirin who received ribavirin but did not occur in any patients who received the ribavirin-free regimen. The ribavirin dose was reduced in accordance with the protocol because of a decreased haemoglobin level in 6 patients with genotype 1a infection who received ribavirin (6.0%); all these patients had a sustained virologic response. [35]

Sub-group analyses of SVR12

On the basis of logistic-regression analyses of baseline demographic and clinical characteristics, only *IL28B* CC genotype, which has historically been associated with increased rates of response to treatment for HCV infection, was associated with an increased rate of sustained virologic response among patients with genotype 1a infection (P = 0.03). [35]

Exploratory outcome measures – HRQoL[47]

A comparison between treatment groups for the mean change from baseline to the final treatment period visit and final post-treatment period visit in PRO scores is presented in Table 50. [redacted] [47]

Table 50: Mean change in PRO scores from baseline to the final treatment period visit and also the post-treatment week 12 visit – PEARL-IV

Instrument	3D + RBV for 12 weeks			3D for 12 weeks		
	N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
SF-36 PCS						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 MCS						

Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L visual analogue score						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L health index score						
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HCV-PRO total score						
Final treatment visit *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Statistically significant difference between treatment groups at $P \leq 0.05$ level.

As previously mentioned, the EQ-5D-5L health index scores have been derived using country specific algorithms to cross-walk the 5L values to the 3L tariff scores. Where an individual country does not have a crosswalk, the US crosswalk to convert the 5L values to 3L has been used. Therefore, the mean health index values for the EQ-5D-5L presented in the table above have been calculated using a number of different countries algorithms, which make the data difficult to interpret. [47]

Treatment compliance

In PEARL-IV, patients took on average at least 98.57% or more of their prescribed doses of each pill (including RBV). [47]

6.5.1.7 Results from AVIATOR - treatment naïve and PegIFN/RBV treatment experienced HCV GT1 patients without cirrhosis

As discussed in Section 6.3, AVIATOR was a phase II dose-finding study comprising 14 treatment arms with different dose combinations of ombitasvir, paritaprevir/r and dasabuvir and different treatment durations. Only arms G and L contain the 3D regimen that is relevant to the proposed licence.[36] In addition, this trial evaluated SVR 24 weeks post-treatment, rather than 12 weeks post treatment like the rest of the trials included in the HCV clinical trial programme. Therefore, this section presents top-line results for information only as data from AVIATOR are not used in the economic model and this trial did not form part of the pivotal trial package submitted to EMA.

Primary outcome measure

Across all treatment subgroups, the rates of SVR24 ranged from 83 to 100% (see

Table 51 below). With respect to the primary analysis, among previously untreated patients who received treatment with 3D + RBV, with ABT-450/r administered as 150 mg of ABT-450 and 100 mg of ritonavir, the rate of sustained virologic response at 24 weeks after treatment was 88% in the subgroup that received 8 weeks of therapy and 95% in the subgroup that received 12 weeks of therapy (difference between 8-week

and 12-week subgroups, −7 percentage points; 95% confidence interval, −19 to 5; P= 0.24).

Table 51: SVR24 rates for each arm in AVIATOR

Cohort	Sub-group	Drug combination	Duration (weeks)	SVR24	
				n/N	% (95% CI)
Treatment naïve patients (N=438)	A	ABT-450/r 150/100 mg +ABT-267 + ABT-333 + ribavirin	8	70/80	87.5 (78-94)
	B	ABT-450/r 150/100 mg + ABT-333 + ribavirin	12	34/41	82.9 (68-93)
	C	ABT-450/r 100/100 mg + ABT-267 + ribavirin	12	33/39	84.6 (69-94)
	D	ABT-450/r 200/100 mg + ABT-267 + ribavirin	12	37/40	92.5 (80-98)
	E	ABT-450/r 150/100 mg + ABT-267 + ABT-333	12	70/79	88.6 (79-95)
	F	ABT-450/r 100/100 mg + ABT-267 + ABT-333 + ribavirin	12	38/39	97.4 (87-100)
	G	ABT-450/r 150/100 mg + ABT-267 + ABT-333 + ribavirin	12	38/40	95.0 (83-99)
	H	ABT-450/r 100/100 mg + ABT-267 + ABT-333 + ribavirin	24	37/40	92.5 (80-98)
	I	ABT-450/r 150/100 mg + ABT-267 + ABT-333 + ribavirin	24	36/40	90.0 (76-97)
Prior null responders (N=133)	J	ABT-450/r 200/100 mg + ABT-267 + ribavirin	12	40/45	88.9 (76-96)
	K	ABT-450/r 100/100 mg + ABT-267 + ABT-333 + ribavirin	12	21/23	91.3 (72-99)
	L	ABT-450/r 150/100 mg + ABT-267 + ABT-333 + ribavirin	12	21/22	95.5 (77-100)
	M	ABT-450/r 100/100 mg + ABT-267 + ABT-333 + ribavirin	24	21/23	91.3 (72-99)
	N	ABT-450/r 150/100 mg + ABT-267 + ABT-333 + ribavirin	24	20/20	100 (83-100)

Secondary outcome measures

In a pre-specified analysis comparing subgroups that received ABT-450/r administered as 100 mg of ABT-450 and 100 mg of ritonavir with those that received ABT-450/r administered as 150 mg of ABT-450 and 100 mg of ritonavir in otherwise identical regimens, the rates of sustained virologic response at 24 weeks were similar (93.6% and 94.3%, respectively; P = 0.91). Therefore, the subgroups differing only in the dose of ABT-450 were combined, which resulted in nine groups for further analysis. With these groups combined, the rates of sustained virologic response at 24 weeks after treatment ranged from 83 to 96% among previously untreated

patients and from 89 to 95% among patients who had not had a response to prior therapy.

Across all treatment groups, the rates of SVR24 were high regardless of host *IL28B* haplotype, HCV subtype, race, or HCV RNA level at baseline. Odds ratios looking at the probability of achieving an SVR response by 5 different patient characteristics are presented in Table 52, and show that only sub-genotype has a significant effect on the probability of response in treatment naïve patients.

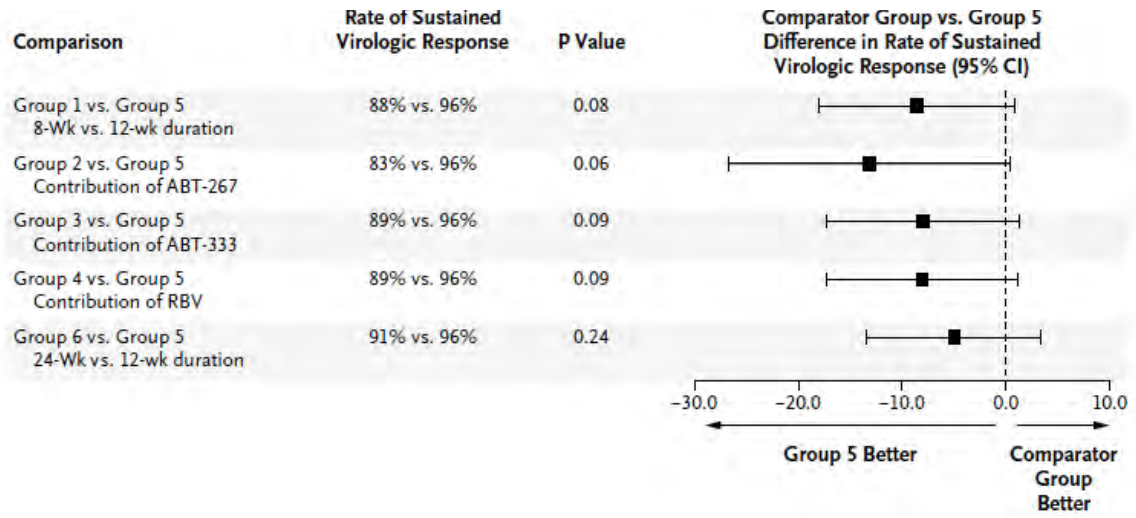
Table 52: SVR24 by subpopulations within each cohort (all subjects)

	Cohort 1: Treatment naïve patients		Cohort 2: Prior null responders	
	Odds Ratio	P value	Odds Ratio	P value
IL28B CC vs. IL28B CT	0.912	0.803	*	*
IL28B CC vs. IL28B TT	1.123	0.794	*	*
Genotype 1a vs. Genotype 1b	1.035	0.0008	0.157	0.083
Black vs. Non-black	1.035	0.941	1.443	0.735
Baseline viral load ≥ 800,000 IU/mL Vs. <800,000 IU/mL	0.600	0.347	†	†

* Not applicable as there is no failure in CC category.
† Not applicable as there is no failure in <800,000 category.
Five subpopulation comparisons were tested in each cohort. All are reported here.

The rates of SVR were highest in the groups that received regimens that included three direct-acting agents plus ribavirin, but comparisons of the group that received three direct-acting agents plus ribavirin for 12 weeks with groups that received two direct-acting agents plus ribavirin did not show significant differences (see Figure 16).

Figure 16: Comparison of SVR24 in treatment naïve subjects from AVIATOR



Note, this figure shows the differences in SVR for Group 5 comprises subjects who received 3D + RBV (not all licensed regimens) for 12 weeks vs. other regimens or duration of treatment.

The rate of SVR24 was higher among previously untreated patients who received three direct-acting agents plus ribavirin for 12 weeks than among those who received the same therapy for 8 weeks (96% and 88%, respectively), but the difference was not significant. Among previously untreated patients who received 3D with ribavirin, relapse after treatment occurred in 12%, 1%, and 2% of patients randomly assigned to 8 weeks, 12 weeks, and 24 weeks of therapy, respectively. None of these patients had virologic breakthrough. Among patients who had not had a response to prior therapy and who received this regimen, there were no relapses among patients treated for 12 weeks or for 24 weeks; 7% and 2% of the patients, respectively, had virologic breakthrough. A 24-week duration of therapy, as compared with a 12-week duration, was not associated with an increase in the rate of sustained virologic response, among either previously untreated patients or patients who had not had a response to prior therapy (P = 0.24 and P = 0.71, respectively).

6.5.1.8 Results from M14-103 - treatment naïve and PegIFN/RBV treatment experienced HCV GT1 patients on stable opioid replacement therapy without cirrhosis

Primary outcome measure

In this phase 2, multicentre, open-label, single arm study, 38 treatment-naïve or PegIFN/RBV treatment experienced, non-cirrhotic subjects with genotype 1 infection who were on stable doses of methadone (N=19) or buprenorphine +/- naloxone (N=19) received 12 weeks of 3D + RBV. Treated subjects had a median age of 51 years (range: 26 to 64); 65.8% were male and 5.3% were Black. A majority (86.8%) had baseline HCV RNA levels of at least 800,000 IU/mL and a majority (84.2%) had genotype 1a infection; 68.4% had IL28B non-CC genotype; 15.8% had portal fibrosis (F2) and 5.3% had bridging fibrosis (F3); and 94.7% were naïve to prior HCV treatment.

Overall, 37 (97.4%) of 38 subjects achieved SVR12 (Table 53).

Table 53: SVR12 for HCV GT1 subjects on stable opioid replacement therapy in M14-103

Treatment outcome	3D + RBV for 12 weeks		
	n/N	%	95% CI
Overall SVR12	37/38	97.4	92.3, 100.0
Outcome for subjects without SVR12			
On-treatment virological failure [a]	0/38	0	
Relapse [b]	0/38	0	
Other [c]	1/38	2.6%	

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other - premature study drug discontinuation due to treatment-emergent adverse events.

Secondary outcome measures

No subject demonstrated on-treatment virologic failure or post-treatment relapse. The most frequent adverse events were nausea, fatigue, and headache. There were no documented dose adjustments of methadone or buprenorphine.

6.5.1.9 Interim results from TURQUOISE-I (M14-004) - treatment naïve and PegIFN/RBV treatment experienced HCV GT1/HIV-1 co-infected patients

Aims and methods

TURQUOISE-I is an ongoing, open-label, randomised phase II/III trial evaluating 3D + RBV for 12 or 24 weeks in adults with HCV GT1/HIV-1 co-infection who are HCV treatment-naïve or PegIFN/RBV-experienced including those with compensated cirrhosis. Estimated enrolment for this study is 300, and the study is currently recruiting patients. Final data collection for the primary outcome is expected September 2015 with the study due to complete May 2016.

However, an interim analysis in 63 patients from the first phase of the study (Part 1a) has been conducted and submitted to EMA as part of the regulatory submission for 3D. In this phase of the study, patients with an unquantifiable plasma HIV-1 RNA and a CD4+ T-cell count ≥ 200 cells/mm3 or CD4+ T-cell % ≥ 14% while on a stable atazanavir (ATV) or raltegravir (RAL) containing HIV-1 anti-retroviral therapy regimen were eligible.

In Part 1a of TURQUOISE-I, 31 subjects were randomised to receive 3D + RBV for 12 weeks in Arm A and 32 subjects received 3D + RBV for 24 weeks in Arm B. Randomised subjects were stratified by prior HCV treatment history (treatment-naïve versus treatment-experienced) and by presence of cirrhosis (cirrhotic or non-cirrhotic). Treatment-naïve subjects were also stratified by interleukin 28B (IL28B) genotype (CC versus non-CC). PegIFN/RBV-experienced subjects were also stratified by type of previous response to PegIFN/RBV. Subjects in Part 1a will be followed for 48 weeks after the end of treatment; however this interim analysis includes available data from Part 1a through to post-treatment week 12.

Patient demographics and participant flow

Treated subjects (N = 63) had a median age of 51 years (range: 31 to 69); 24% of subjects were Black; 81% of subjects had IL28B non-CC genotype; 19% of subjects had compensated cirrhosis; 67% of subjects were HCV treatment-naïve; 33% of subjects had failed prior treatment with PegIFN/RBV; and 89% of subjects had HCV genotype 1a infection.

Among Part 1a subjects randomised to Arm A (12-week treatment), 30 out of 31 subjects completed treatment; 1 subject prematurely discontinued the study due to withdrawal of consent prior to treatment completion. Among the 32 subjects randomised to Arm B (24-week treatment), 31 completed treatment; 1 subject prematurely discontinued study treatment due to on-treatment HCV virologic failure prior to treatment completion (rebound).

Results

In TURQUOISE-I, the SVR12 rates in HCV/HIV-1 co-infected subjects were consistent with SVR12 rates in the phase 3 trials of HCV mono-infected subjects. Seven of 7 (100%) subjects with genotype 1b infection and 51 of 56 (91.1%) subjects with genotype 1a infection achieved SVR12. Five of 6 subjects with compensated cirrhosis in each arm achieved SVR12 (see Table 54).

Table 54: SVR12 for HCV GT1/HIV-1 co-infected subjects from TURQUOISE-I

Treatment outcome	3D + RBV for 12 weeks			3D+ RBV for 24 weeks		
	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	29/31	93.5	79.3,98.2	29/32	90.6	75.8, 96.8
Subgroup						
GT1a	25/27	93		26/29	90	
GT1b	4/4	100		3/3	100	
Cirrhotic	5/6	83		5/6	83	
Non-cirrhotic	24/25	96		24/26	92	
Outcome for subjects without SVR12						
On-treatment virological failure [a]	0	0		1	3.1	
Relapse [b]	1	3.2		2[c]	6.25	
Other [d]	1	3.2		0	0	

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. These virologic failures appear to have resulted from reinfection based on analyses of baseline and virologic failure samples

d. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Safety

The overall safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. No subject in either arm experienced a treatment-emergent serious adverse event or discontinued study drug due to any treatment-emergent adverse event. The most common treatment-emergent adverse event occurring in ≥ 20.0% of subjects in both arms combined was fatigue.

No subject experienced a grade 3 ALT elevation. Transient elevations in total bilirubin >3 x ULN (mostly indirect) occurred in 17 (27.0%) subjects; 15 of these subjects were receiving atazanavir. None of the subjects with hyperbilirubinaemia had concomitant elevations of aminotransferases (see section 4.8). All of the 6 subjects who required ribavirin dose reduction for management of anaemia achieved SVR12.

No subjects in either treatment arm required a switch of their HIV-1 ART regimen due to loss of plasma HIV-1 RNA suppression. Median declines in the CD4+ T-cell counts of 47.0 and 62.0 cells/mm^3 were observed at the end of 12 and 24 weeks treatment respectively, but returned to baseline post-treatment. CD4 percentages remained stable throughout the treatment period.

6.5.1.10 Interim results from CORAL-I (M12-999) – HCV GT1 post-transplant patients

Aims and methods

CORAL-I is an ongoing, phase II, open-label, multi-centre study evaluating the safety and efficacy of 3D with and without ribavirin in adult liver transplant recipients with recurrent HCV GT1 infection. Estimated enrolment for this study is 70 patients, and the study is currently recruiting. Final data collection for the primary outcome is expected December 2015 with the study due to complete February 2016.

The study design includes 2 cohorts of subjects: Cohort 1 (consisting of Arm A) and Cohort 2 (consisting of Arms B and C). Enrolment in Arm A is complete, with 34 subjects at 10 sites in the United States and Spain. Interim data for Cohort 1 is available and was submitted to EMA as part of the regulatory filing for 3D – it is therefore included here.

Cohort 1 comprises 34 HCV genotype 1-infected subjects with fibrosis ≤ F2 (Metavir). Subjects were treatment-naïve after transplantation but may have received previous HCV treatment (PegIFN or IFN with or without RBV) prior to liver transplantation. These subjects were assigned to receive 24-week treatment with 3D with ribavirin and were then followed up for 48 weeks. The dose of ribavirin was left to the discretion of the investigator, with most patients receiving 600 to 800 mg per day as a starting dose, and most patients also receiving 600 to 800 mg per day at the end of treatment.

Patient demographics and participant flow

Thirty-four subjects were randomised and received study drug in Arm A; 33 subjects completed study drug and 1 subject discontinued study drug after Week 18 due to an adverse event.

The majority of the subjects were male (79.4%) and white (85.3%), with 50.0% having a body mass index (BMI) ≥ 30 kg/m2. The majority of subjects were also infected with HCV genotype 1a (85.3%) and were IL28B non-CC genotype (76.5%). The mean time since liver transplantation was approximately 4 years.

With regard to immunosuppression medication at baseline, 29 (85.3%) subjects were taking tacrolimus and 5 (14.7%) subjects were taking cyclosporine. Eleven (32.4%) subjects were also taking mycophenolic acid and 2 (5.9%) subjects were taking

prednisone prior to the first study drug dose. Most subjects (97.1%) took a prior (before the first study drug dose) medication. The most common (≥ 5 subjects) prior medications included acetylsalicylic acid (19 subjects; 55.9%), multivitamin (13 subjects; 38.2%), amlodipine (12 subjects; 35.3%), magnesium (9 subjects; 26.5%), omeprazole (9 subjects; 26.5%), metoprolol (5 subjects; 14.7%), and calcium carbonate (5 subjects; 14.7%).

Results

All 34 subjects (100%) in Arm A achieved both rapid virologic response and an end-of-treatment response. Thirty-three of 34 subjects (97.1%) achieved SVR12; 96.6% (28/29) in subjects with genotype 1a infection and 100% (5/5) in subjects with genotype 1b infection (see Table 55). A single subject with HCV genotype 1a infection experienced relapse at Post-Treatment Day 3 and failed to achieve SVR12.

Table 55: SVR12 for HCV GT1 post liver transplant subjects in M12-999

Treatment outcome	3D +/- RBV for 24 weeks		
	n/N	%	95% CI
Overall SVR12	33/34	97.1	-
Subgroup			
GT1a	28/29	96.6	
GT1b	5/5	100	
Outcome for subjects without SVR12			
On-treatment virological failure [a]	0	0	
Relapse [b]	1	2.9	
Other [c]	0	0	

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

6.5.1.11 Results from PEARL-I (M13-393) – treatment naïve and PegIFN/RBV treatment experienced HCV GT4 patients without cirrhosis

As discussed in Section 6.3, the primary objective of this study was two-fold – to look at the safety and efficacy (SVR12) of:

- 2D
  - among treatment-naïve and prior PegIFN/RBV null responder HCV GT1b-infected subjects without cirrhosis and
  - among treatment-naïve and PegIFN/RBV treatment-experienced HCV GT1b-infected subjects with compensated cirrhosis
- 2D with or without RBV

- among treatment-naïve and PegIFN/RBV treatment-experienced HCV GT4-infected subjects.

The proposed regimen for patients with HCV GT1b is to use 3D (paritaprevir/r + ombitasvir + dasabuvir) and not 2D (paritaprevir/r + ombitasvir) as was used in this trial. Therefore, this section only presents results from the HCV GT4 study arms of PEARL-I, as the study arms in patients with GT1b do not use the correct regimen for this patient population and are therefore not relevant to the decision problem (see Table 31 for study design).

Primary outcome measure

Table 56 provides SVR12 rates for genotype 4 infected subjects, treatment-naïve or previously treated with PegIFN/RBV, who received 2D with or without ribavirin for 12 weeks in PEARL I.

Table 56: SVR12 for genotype 4-infected subjects who were treatment-naïve or previously treated with PegIFN/RBV in PEARL-I

Treatment outcome	2D for 12 weeks								
	Treatment naive						PegIFN/RBV-experienced		
	Without RBV			With RBV			With RBV		
	n/N	%	95% CI	n/N	%	95% CI	n/N	%	95% CI
Overall SVR12	40/44	90.9%	78.3, 97.5	42/42	100%	91.6, 100	49/49	100%	92.7, 100
Outcome for subjects without SVR12									
On-treatment virological failure [a]	1/44	2.3%		0/42	0		0/49	0	
Relapse [b]	2/44	4.5%		0/42	0		0/49	0	
Other [c]	1/44	2.3%		0/42	0		0/49	0	

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

The reasons for the 4 nonresponses in Group 1 (2D alone) were on-treatment virologic failure due to rebound for 1 subject, post-treatment relapse for 2 subjects, and premature discontinuation of study drug for 1 subject. As a sensitivity analysis, the SVR12 rates were calculated without imputation of missing values and there was no change in the results.

The unadjusted SVR12 rate in Group 1 was lower than the SVR12 rate in Group 4 by 9.09% (95% CI: 0.60, 17.59). When the Mantel-Haenszel method was used to adjust the comparison for differences in the proportion of IL28B CC subjects (versus non-CC), the estimate of the difference increased slightly to 9.16% (95% CI: –1.29, 19.61); however, the width of the 95% confidence interval increased to include zero, which would represent no statistically significant difference in SVR12 rates between the groups.

Secondary outcome measures

- Percentage of subjects with SVR24

SVR24 was achieved in 86.4% (38/44; 95% CI: 72.6, 94.8) of treatment-naïve GT4-infected subjects treated with 2D (Group 1) and 97.6% (41/42; 95% CI: 87.4, 99.9) of treatment-naïve subjects treated with 2D + RBV (Group 4). No new relapses were observed after Post-Treatment Week 12 for subjects with data. The reasons for the 6 non-responses in Group 1 were on-treatment virologic failure due to rebound for 1 subject, relapse by Post-Treatment Week 12 for 2 subjects, premature discontinuation of study drug for 1 subject, and missing SVR24 data for 2 subjects. The reason for the 1 non-response in Group 4 was missing SVR24 data. The SVR24 results were not summarised for treatment-experienced subjects treated with 2D + RBV (Group 6) because this treatment group was ongoing and had not completed Post-Treatment Week 24 at the time of the database lock.

The unadjusted SVR24 rate in Group 1 was lower than the SVR24 rate in Group 4 by 11.26% (95% CI: 0.12, 22.39). When the Mantel-Haenszel method was used to adjust the comparison for differences in the proportion of IL28B CC subjects (versus non-CC), the estimate of the difference increased slightly to 11.38% (95% CI: –1.12, 23.87), however, the width of the 95% confidence interval increased to include zero, which would represent no statistically significant difference in SVR24 rates between the groups.

- Virologic failure and post-treatment relapse

No treatment-naïve or treatment-experienced GT4-infected subject treated with 2D + RBV (Groups 4 and 6) experienced virologic failure during the treatment period or experienced a relapse during the post-treatment period as of the data cut-off date, at which time Group 4 had completed through to post-treatment week 24 and Group 6 had completed through to post-treatment week 12.

In the treatment-naïve group treated with 2D alone (Group 1), 1 of the 44 subjects experienced on-treatment virologic failure and 2 subjects relapsed within 12 weeks post-treatment (1 relapse occurred within 4 weeks post-treatment). Group 1 had completed post-treatment week 24 as of the data cut-off date. Based on the phylogenetic analysis of baseline samples, all 3 subjects who experienced on-treatment virologic failure or relapse were infected with HCV subtype 4d.

Sub-group analyses of SVR12

All HCV GT4-infected subjects treated with 2D + RBV (100%) achieved SVR12, and thus the SVR12 rate did not differ across subgroups.

Exploratory outcome measures [39]

[redacted]

[redacted]

Table 57: Mean change from baseline to final treatment visit and post-treatment week 24 from GT4 subjects in PEARL-I

Assessment visit/ Group	N	Baseline mean	Mean change from baseline (SD)	Gp 1 vs. Gp 4 difference, LS mean (95% CI) P value
HCV-PRO total score				
Final treatment visit				
Group 1 (tx-naïve, 2D)	[redacted]	[redacted]	[redacted]	[redacted]
Group 4 (tx-naïve, 2D + RBV)	[redacted]	[redacted]	[redacted]	
Group 6 (tx-experienced, 2D + RBV)	[redacted]	[redacted]	[redacted]	
Post -treatment week 24				
Group 1 (tx-naïve, 2D)	[redacted]	[redacted]	[redacted]	[redacted]
Group 4 (tx-naïve, 2D + RBV)	[redacted]	[redacted]	[redacted]	
EQ-5D-5L Health Index score				
Final treatment visit				
Group 1 (tx-naïve, 2D)	[redacted]	[redacted]	[redacted]	[redacted]
Group 4 (tx-naïve, 2D + RBV)	[redacted]	[redacted]	[redacted]	
Group 6 (tx-experienced, 2D + RBV)	[redacted]	[redacted]	[redacted]	
Post -treatment week 24				
Group 1 (tx-naïve, 2D)	[redacted]	[redacted]	[redacted]	[redacted]
Group 4 (tx-naïve, 2D + RBV)	[redacted]	[redacted]	[redacted]	

As previously mentioned, the EQ-5D-5L health index scores have been derived using country specific algorithms to cross-walk the 5L values to the 3L tariff scores. Where an individual country does not have a crosswalk, the US crosswalk to convert the 5L values to 3L has been used. Therefore, the mean health index values for the EQ-5D-5L presented in the table above have been calculated using a number of different countries algorithms, which make the data difficult to interpret.

Treatment compliance

All subjects (100%) were compliant with 2D + RBV (Groups 4 and 6) treatment. For ritonavir, all subjects (100%) in Groups 2, 6, 7, and 8 were compliant, and 93.0% compliance was achieved in Group 1.

6.6 Meta-analysis

6.6.1 **The following steps should be used as a minimum when presenting a meta-analysis.**

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**
- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis when appropriate.**
- **Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).**

There is only one trial evaluating 2D in patients with HCV GT4, so there is no need to undertake a meta-analysis for this genotype.

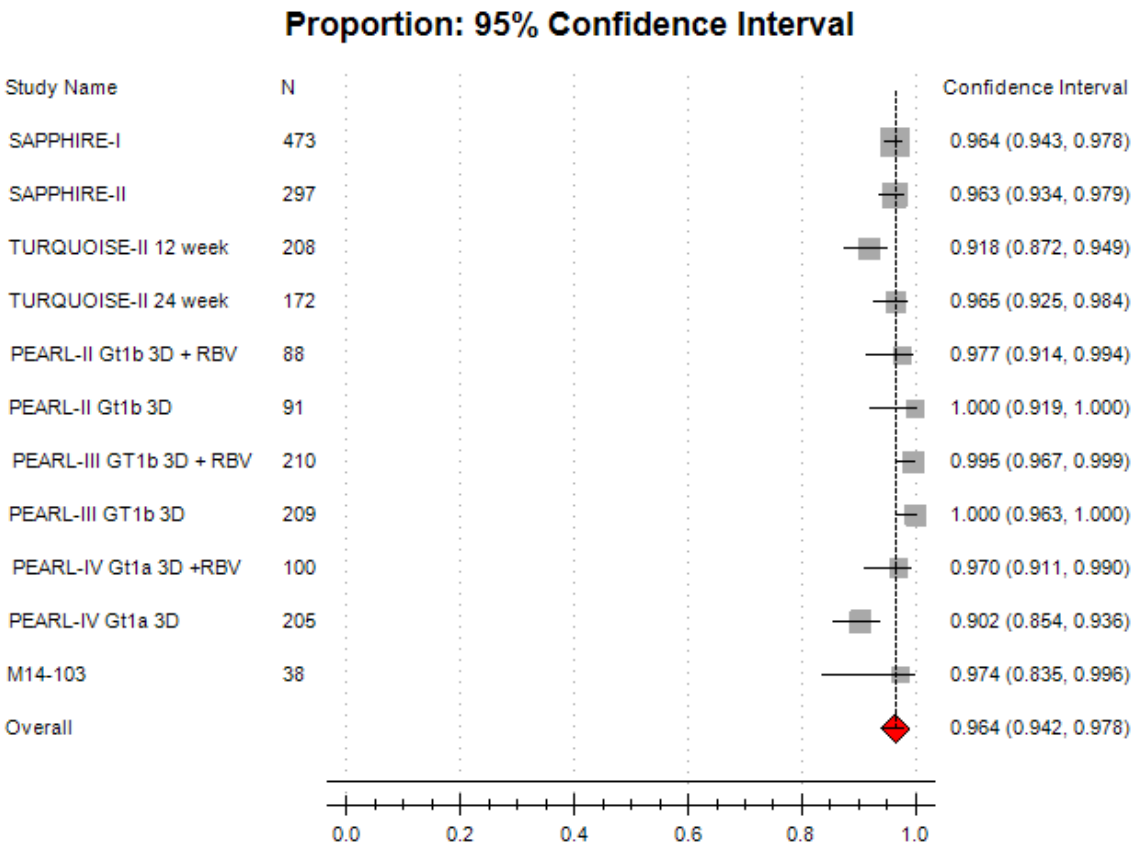
There are six completed phase III trials and two phase II trials evaluating 3D in patients with HCV GT1 presented in Section 6.5. Contrary to traditional HCV antiviral agents where the study populations comprised a mixture of HCV patient characteristics (e.g. a mixture of GT1a, GT1b, cirrhosis etc), the majority of AbbVie's clinical trials were conducted in HCV GT1 patients with specific characteristics known to affect the probability of response e.g. TURQUOISE-II was conducted in 100% patients with compensated cirrhosis; PEARL-II was specifically in PegIFN/RBV experienced GT1b patients but excluding those with cirrhosis; PEARL-IV was specifically in treatment naïve HCV GT1a patients, again excluding cirrhotic patients.

Therefore, it is clear without having to perform statistical assessments of heterogeneity that the trials are highly heterogenic in terms of patient characteristics at baseline e.g. 0% cirrhosis in the SAPPHIRE and PEARL trials vs. 100% in TURQUOISE-II; or 100% GT1a in PEARL-IV vs 100% GT1b in PEARL-III; or 100% treatment naïve in SAPPHIRE-I vs 100% treatment-experienced in SAPPHIRE-II. As a result of this heterogeneity, pooled estimates of SVR might not be appropriate.

Furthermore, as discussed in Section 6.3 and 6.5, the HCV GT1 clinical trial programme was designed and powered to assess the non-inferiority and superiority of 3D vs historical telaprevir SVR rates. As such, the trials do not have a reference arm or control arm in order to calculate the absolute or relative risk reduction. In the SAPPHIRE trials no efficacy outcomes were collected in the initial 12 week placebo arm of the trials, therefore the active arms have been treated like single arm studies. In TURQUOISE-II, the two arms comprised different treatment durations of 3D (12 week and 24 weeks) not a control arm. The three PEARL studies were all two arm trials, but evaluated 3D alone vs 3D + RBV - again no control or comparator arm to calculate the relative or absolute risk reduction.

Therefore, to at least attempt to generate a pooled estimate of SVR for the 3D HCV GT1 clinical trial programme, AbbVie has used Meta-Analyst software,[48] which allows a pooled estimate of efficacy to be generated from single arm studies. Instead of calculating the relative risk or odds ratio of one arm vs. another, each arm can be included individually generating an individual SVR point estimate and associated 95% CIs. These can subsequently be pooled using either a fixed or random effects model to generate an overall estimate of efficacy. Figure 17 presents the forest plot of SVR12 rates from all the arms in the 3D HCV GT1 clinical trial programme using a random effects model.

Figure 17: Forest plot of SVR12 rates for 3D from the active arms in the HCV GT1 completed phase III clinical trials (and the phase II opioid study)



	Median	Min	Max	p25	p75
Sample Size	205	38	473	95.500	209.500
Effect Size	0.970	0.902	0.998	0.964	0.986

	Estimate	95% Confidence Interval		Tau-Squared	H	I^2	Q	DF	P-value
Pooled	0.964	0.942	0.978	0.275	0.645	0.411	0.971	0.909	0.000

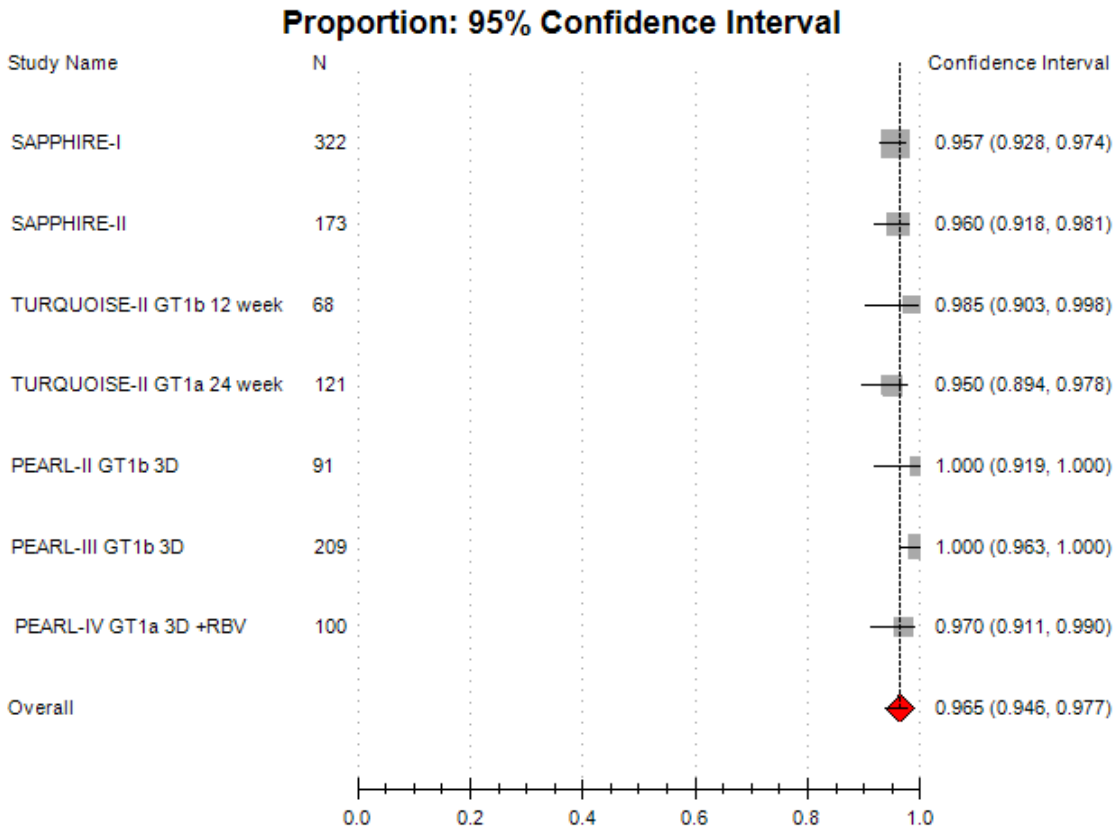
As can be seen from this figure, there are data in over 2,000 HCV GT1 subjects contributing to the overall estimate of SVR12 – 96.4% (95% CI: 0.942, 0.978; binary random effects). A fixed effects model produced a similar estimate to that observed using a random effects model, but had tighter confidence intervals – higher precision

around the point estimate. However, given the heterogeneity in the HCV trial programme, the random effects model was considered to be a better fit.

It should be noted that this meta-analysis pools data for all arms of the trials presented in Section 6.5.1. However, the pooled estimate includes data for arms that contain unlicensed combinations of 3D. For example, for treatment naïve or treatment-experienced GT1b patients, the licence states that 3D should be given alone and not in combination with RBV. Therefore, both the SAPPHIRE trials in patients with GT1b, and the 3D + RBV arms in PEARL-II and PEARL-III are outside of the licence. Similarly, for GT1a patients with cirrhosis, patients should receive 24 weeks of 3D + RBV and not 12 weeks, and therefore a proportion of patients from the 12 week arm of TURQUOISE-II are outside of the licence.

The economic model and all the data inputs in Section 7 utilise only the licensed data in the efficacy estimates. Figure 18 below shows the forest plot specifically for trial arms that are in line with the licence for 3D and excludes all other arms. As can be seen from Figure 18, the overall SVR changes very little from 96.4% (95% CI: 0.942, 0.978) to 96.5% (95% CI: 0.946, 0.977) because the SVR data are consistently high for 3D.

Figure 18: Forest plot of SVR12 rates from the completed phase III trials in line with the licence for 3D in HCV GT1



	Median	Min	Max	p25	p75
Sample Size	121	68	322	95.500	191
Effect Size	0.970	0.950	0.998	0.958	0.990

	Estimate	95% Confidence Interval		Tau-Squared	H	I^2	Q	DF	P-value
Pooled	0.965	0.946	0.977	0.072	0.531	0.182	0.885	0.857	0.206

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

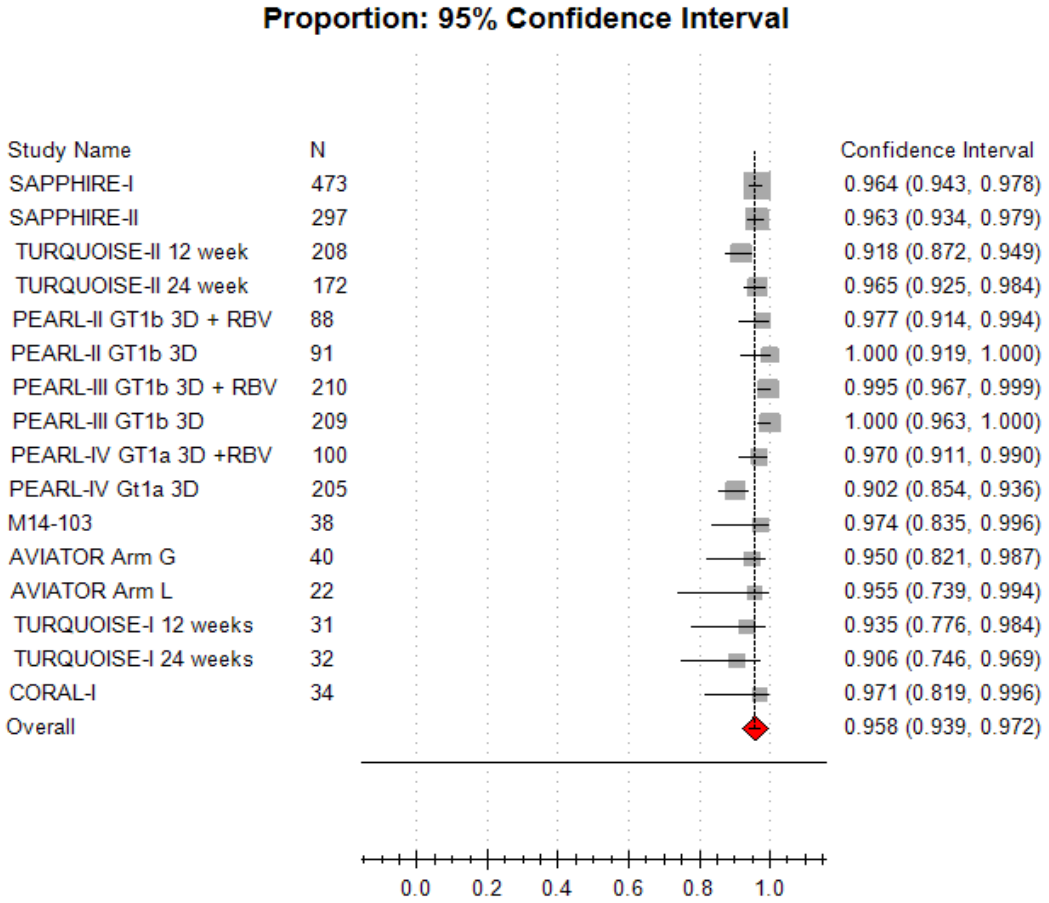
Section 6.6.1 provides a meta-analysis of the 3D HCV GT1 clinical trials to give a pooled SVR12 estimate of 96.4%, irrespective of the different proportions of patients who were treatment naïve, treatment experienced, cirrhotic, GT1a or GT1b included in the trials. Given that AbbVie's clinical trial programme was designed to assess the efficacy of 3D in HCV patients with specific characteristics e.g. TURQUOISE-II was a 100% cirrhotic trial and PEARL-III was conducted specifically in GT1b naïve patients excluding cirrhotics, the trials are highly heterogenic and so technically should probably not be pooled.

The SVR12 rates for 3D are consistently high regardless of the fact that the trials are vastly different in terms of patient characteristics as can be seen from Figure 17, which is a benefit of AbbVie's regimen. However, one of many reasons an indirect comparison could not be performed (discussed in detail in Section 6.7) is because these patient characteristics have a significant impact on the probability of achieving an SVR for the traditional agents like PegIFN/RBV, boceprevir, and telaprevir; and also for some newer agents like simeprevir. The data would need substantial adjustment to make the trial populations similar enough to allow for an indirect comparison, which given the limited number of trials connected in the network is extremely difficult (see Section 6.7).

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

The only completed trial that has been excluded from the meta-analysis is the dose finding phase II study – AVIATOR, because it includes arms with different combinations, different doses and different treatment durations to that of the combination, dose and duration used in the pivotal phase III studies. In addition, interim data for the two ongoing trials in HCV GT1/HIV-1 co-infected individuals (TURQUOISE-I) and the post-transplant study (CORAL-I) have also not been included in the meta-analysis as they have not finished recruiting and therefore are not yet sufficiently powered and/ or completed. Furthermore, they have not been included in Section 6.2.4. However, to test the impact of excluding these trials on the overall estimate of efficacy, Figure 19 below shows the forest plot with these trials included. The figure shows that there is very little change in the overall point estimate when these trials are included.

Figure 19: Forest plot of SVR12 rates for 3D from all the active arms in the HCV GT1 clinical trial programme (completed and interim results)



	Median	Min	Max	p25	p75
Sample Size	95.500	22	473	37	208.250
Effect Size	0.965	0.902	0.998	0.946	0.975

	Estimate	95% Confidence Interval		Tau-Squared	H	I^2	Q	DF	P-value
Pooled	0.958	0.939	0.972	0.218	0.603	0.362	0.972	0.938	0.003

6.7 *Indirect and mixed treatment comparisons*

There are currently no head-to-head RCTs evaluating either 3D or 2D in patients with HCV, therefore AbbVie investigated the feasibility of conducting an indirect treatment comparison - specifically a network meta-analysis (NMA) - to generate relative estimates of efficacy for AbbVie's regimens vs. the comparators outlined in the decision problem. Head-to-head data versus telaprevir will be available from the MALACHITE studies during the course of this appraisal; however this will only be for the non-cirrhotic patient subgroups.

AbbVie encountered a number of insurmountable problems, explained in Sections 6.7.1-6.7.3 below that meant that the results from the NMA could not be considered robust. It was therefore considered appropriate to populate the economic base case with efficacy data directly reported from the clinical trials in enough granularity to ensure that specific patient characteristics known to affect the probability of achieving an SVR are separated out. For instance, the model requires that SVR data are split out by fibrosis status, sub-genotype, and type of treatment response e.g. naïve, relapser, partial responder or prior null responder. As an example of this, SVR data for HCV GT1a cirrhotic null responders in AbbVie's regimens are compared to SVR data for HCV GT1a cirrhotic null responders for the competitor regimens in equal proportions; or treatment naïve GT1b non-cirrhotic patients with mild fibrosis are compared in equal proportions to treatment naïve GT1b non-cirrhotic patients with mild fibrosis in the competitor regimens (see economic model for structure and treatment library).

By adopting this approach, AbbVie has attempted to ensure that the differences observed across the studies only reflects the difference between treatments and not the differences in patient characteristics. AbbVie recognises that this is not an ideal approach. However given that any network meta-analysis involving disconnected nodes would require either a) relying on some very strong assumptions that are likely to be violated based on the data, or b) rely on the synthesis of dummy comparator arms that increases the uncertainty in the estimates anyway, AbbVie concluded that for all the reasons discussed below a network-meta-analysis was not appropriate.

6.7.1 Disconnected network and appropriate NMA methodology

The most commonly used approach for a NMA and the approach NICE prefers is the treatment-effect (TE) model, modelling the relative effect of each intervention within each study. It has the advantage of preserving the randomisation within each study, which ensures that the difference observed between arms only reflects the difference between treatments and not differences in patient characteristics. For this reason, TE models are generally less prone to bias due to model misspecification and variability in prognostic factors than other types of models. However, a TE model requires that the included studies are designed with a comparator arm or 'reference' treatment arm; and the most common of these comparator arm forms the reference treatment in a network allowing pairwise comparisons of all treatments of interest within the network.

As discussed in detail in Sections 6.4 and 6.5, although AbbVie's HCV GT1 clinical trial programme has been conducted in over 2,000 subjects to date and the majority of the trials were double-blind RCTs, they were designed and powered to detect the inferiority and subsequent superiority of 3D vs. historical telaprevir + PegIFN/RBV

SVR data, where the randomised arms are for example 3D with or without ribavirin, or 12 vs 24 weeks of treatment. Therefore, there are no reference or comparator arms in AbbVie's trials that enable 3D to link into a network of evidence of other treatments for HCV GT1.

Unfortunately, TE models are not able to handle disconnected networks or single-arm studies without having to make up the missing connections, for example by synthesising dummy comparator or 'placebo' arms or sourcing the data from non-RCT sources e.g. observational studies. For HCV GT1, one option would be to synthesise a dummy comparator arm (PegIFN + RBV) for all the single-arm studies, based on the distribution of patient characteristics of the single arm, and then obtain relative estimates of efficacy.

Initially, the PegIFN + RBV efficacy data would be estimated from a meta-regression of all the PegIFN + RBV trial data, so that the co-efficients for race, age, cirrhotic status, sub-genotype, reason for prior treatment failure, weight, viral load etc. would all contribute to the estimated SVR rates. The co-efficients for each characteristic generated from the meta-regression would then be used to generate the dummy PegIFN/RBV data such that the predicted PegIFN/RBVSVR results would be adjusted by the spread of patient characteristics from each single arm trial. In this way the distribution of the patient characteristics from all the trials within the network would be preserved, so that a trial with fewer unfavourable patient characteristics would result in a higher estimate of efficacy for PegIFN +RBV (e.g. 57%), but a trial with a high proportion of unfavourable characteristics like null responders or cirrhosis would result in a lower estimate for PegIFN + RBV (e.g. 21%).

It would then be possible to calculate the relative effectiveness of AbbVie's regimens vs. these dummy PegIFN + RBV arms; and similarly for other regimens which have the same problems. The second stage would then be to calibrate all the different PegIFN + RBV estimates to create a common single estimate and link AbbVie's regimen within the network that way.

The benefit of this methodology is that it preserves the different patient characteristics between the trials i.e. the between trial heterogeneity is accounted for, and it would be reasonable to suggest that the differences observed across the studies reflects the difference between treatments and not the differences in patient characteristics. The big disadvantage of this methodology is that it relies on the assumption that SVR for PegIFN/RBV is predictable based on the current set of evidence – i.e. that all characteristics that affect the probability of achieving and SVR known and accounted for. Furthermore, because the covariates will be generated from a meta-regression based on a systematic review of the PegIFN/RBV SVR data, and not patient level data, there is the risk of ecological bias. Secondly, relative effectiveness of the regimens in the single arm studies would be calculated from a synthesised cohort with matching characteristics, increasing the level of uncertainty and potential for bias in the efficacy estimates. As a result of these two limitations, AbbVie felt that it would be more transparent to use SVR data directly reported from the trials and instead analyse the trial designs and patient populations to identify areas of bias that may affect the results (see Section 6.9 interpretation of clinical evidence).

An alternative approach to conducting a NMA with disconnected nodes, is to use a treatment response (TR) model. A TR approach models the absolute probability of achieving the outcome with each intervention. In its simplest form, such a model can be considered as an extension of the simple naive indirect comparison, which crudely compares the average performances of each treatment as if they were all part of the

same study. By disregarding randomisation, bias due to differences in study and patients characteristics may be introduced, which is why the naive indirect comparison is not considered an appropriate method by NICE for determining relative estimates of effect. The incorporation of intra-trial correlations in a TR model improves the approach and makes the methodology more robust. Whilst such a model allows for a more flexible shape of the network, unfortunately it relies on a number of strong assumptions on the treatment effects (consistency, exchangeability) and on the variances (pairwise relative effects are equally variable across studies, yet the "true" placebo effect never varies).

For the TR approach, under the consistency assumption, the difference between treatments, A and B, minus the difference between treatments A and C is equal to the difference between treatments B and C. This is related to the concepts of transitivity, similarity and exchangeability: broadly, it is assumed that if, for example, an additional arm involving treatment C was added to any of the trials comparing A and B, that the difference would be the same as if measured using indirect techniques. The consistency assumption would be violated if factors that could influence the scale-specific outcome are distributed unevenly across the network.

As discussed in Section 6.6, AbbVie designed its clinical trial programme to look at the safety and efficacy of 3D in specific patient populations e.g. TURQUOISE-II was conducted in 100% cirrhotic patients (N=380), or PEARL-III - a trial looking at 3D only in treatment naïve HCV GT1b patients. This is very different to the trials for the comparator regimens outlined in the decision problem, which contain mixed HCV GT1 populations where the proportion of cirrhotic patients varies from around 4% up to 30%, and the percentage of GT1b patients varies from 23% up to 72% of the total trial population. This wouldn't necessarily be an issue if it wasn't well documented that there are known predictive factors that affect the probability of achieving an SVR like HCV GT1 sub-genotype, type of response to prior treatment, or the cirrhotic status of a patient. To complicate matters further, these characteristics are treatment-specific and the magnitude of the impact the specific characteristic has on achieving an SVR varies across treatments (see Section 6.7.3 for illustrations of this point).

It is therefore clear that the consistency and exchangeability assumption is violated in the HCV NMA TR approach, unless some form of specific covariate adjustment could be implemented to account for the uneven distribution of these known factors.

6.7.2 Including adjustment factors into an NMA TR model

Given the uneven distribution of factors known to affect the probability of achieving an SVR in the network of evidence, AbbVie attempted to do some form of covariate adjustment using the TR model to account for these differences. However, the number of coefficients in a model is typically limited by the number of observed data points. Often, a single common coefficient is used to accommodate smaller networks of evidence. The problem with the HCV network of evidence is that there are a number of disconnected nodes and the actual network of evidence is quite sparse; yet multiple covariate adjustments are required for sub-genotype, treatment experience, cirrhosis status etc.

In situations such as sparse networks like this one, where prior distributions (either informed or uninformed) may dominate, the validity of the network meta-analysis outputs will depend on the validity of prior distribution placed on the co-efficient. Given the fact that the prior distributions could not be based on the data used to inform the posterior distribution, and in the absence of any other data, uninformed priors were used. This led to meaningless outputs where the data lacked

convergence; even attempting a common covariate adjustment rather than a treatment specific effect did not achieve convergence in the model.

The only outputs from the TR model that converged were the unadjusted SVR data, which violate the consistency and exchangeability assumption needed for a TR model because of the uneven distribution of predictive patient characteristics across the trials. An unadjusted output in this case is equivalent to a naive indirect comparison anyway.

Therefore, based on the problems with both the TE model and the TR model in a disconnected network discussed above, in the base case AbbVie used efficacy data directly reported from the clinical trials in enough granularity to ensure that specific patient characteristics known to affect the probability of achieving an SVR are separated out.

6.7.3 Analysis of the impact specific patient characteristics have on the probability of an SVR

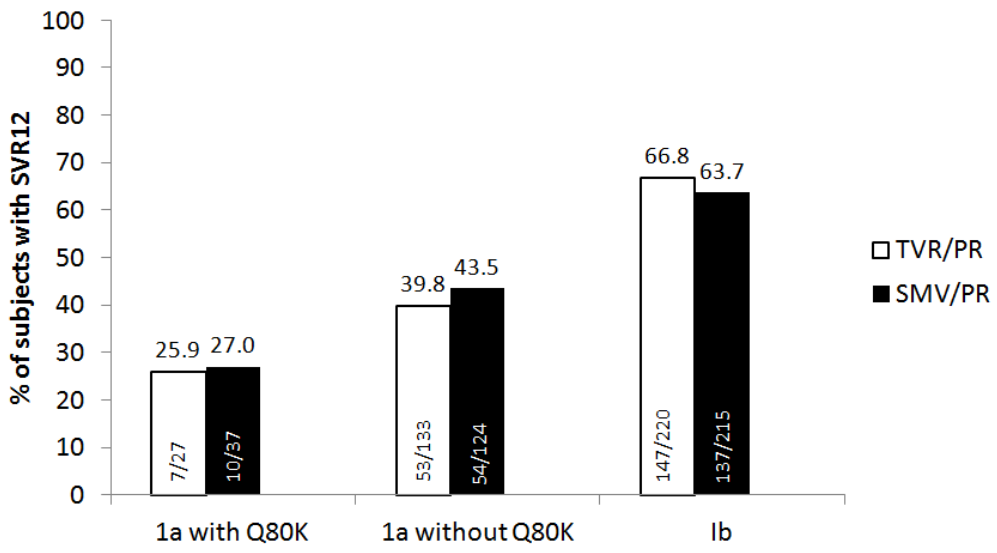
As discussed in Sections 6.6.2 and 6.7.1 above, it is well documented that there are known predictive factors that affect the probability of achieving an SVR like HCV GT1 sub-genotype, type of response to prior treatment, or the cirrhotic status of a patient. Furthermore, the magnitude of the impact the specific characteristic has on achieving and SVR varies across treatments making any network meta-analysis very challenging in this disease area.

A treatment effect model will mitigate the impact of some of these characteristics, particularly for characteristics that have a common effect on all treatments, as the calculation of relative effectiveness will cancel out the impact a common covariate has on the probability of response. However, in HCV many of the predictive factors lead to a treatment specific effect, such that in an indirect comparison, treatments with a high proportion of favourable characteristics may artificially appear to have superior SVR rates, when in actual fact the difference in efficacy estimates are down to the difference in the spread of treatment specific characteristics across the trials. For example, what if we needed to know the relative effectiveness of treatment A vs. treatment C, but only trials of A vs. B and B vs. C exist. Also, what if 72% of the population in the trial of A vs. B are GT1b infected patients whereas only 23% of the trial of B vs. C are GT1b patients. Importantly, what if sub-genotype as a characteristic has little impact on the probability of an SVR for treatment B, but makes a huge difference to treatments A and C. Unless there is some form of meta-regression to adjust for these differences, it is unclear whether the differences between A and C inferred from an indirect comparison are attributable to a difference in efficacy between the two treatments, or as a result of the difference in characteristics between the trials.

A good example of this is in the indirect comparison submitted as part of the manufacturer submission (MS) for simeprevir to NICE.[19] The licence for simeprevir stipulates that GT1a infected patients with the Q80K polymorphism should use an alternative therapy to simeprevir. Therefore the SVR estimates generated from the MTC quite rightly only used SVR data from their licensed population, which excluded GT1a Q80K positive patients. Yet, for all the other comparators the SVR data for the ITT populations from the trials were used. When looking at Figure 14 on page 55 of the MS, see Figure 20 below) which presents SVR data by sub-genotype and genotype 1a Q80K polymorphism for simeprevir vs. telaprevir from the ATTAIN trial, it is interesting to see that telaprevir SVR rates are not only affected by sub-

genotype, but also by Q80K polymorphism status. There is a 16.5% reduction in SVR for GT1a Q80K positive patients for simeprevir and a 13.5% reduction in SVR for GT1a Q80K positive patients for telaprevir vs. GT1a Q80K negative patients. Therefore, by selecting only Q80K negative GT1a SVR data for simeprevir, but not doing the equivalent for telaprevir, means that it is not possible to discern whether the differences in SVR reported in the MTC output between simeprevir and telaprevir are attributable to actual differences of the drugs or whether this is just down to the inclusion and exclusion of Q80K positive patients.

Figure 20: SVR rates in genotype 1a Q80K negative and positive from the ATTAIN trial of simeprevir vs. telaprevir (Figure 14, page 55 of MS)



Another example looking at the different impact certain characteristics have on the probability of achieving an SVR is illustrated in Table 58 below. This table presents SVR data for 3D, PegIFN/RBV, telaprevir, boceprevir, sofosbuvir and simeprevir in HCV GT1 treatment naïve non-cirrhotic patients, arguably the easiest to treat population, through to HCV GT1 infected patients with compensated cirrhotics who were also null responders to previous PegIFN/RBV therapy, arguably the hardest to treat HCV GT1 population. Whilst AbbVie acknowledges that the n numbers are small for some of the comparator agents, the impact these disease characteristics have on the probability of achieving an SVR is apparent immediately.

Table 58 shows that AbbVie's regimen is not affected by any of these characteristics, with 96.8% HCV GT1 treatment naïve non-cirrhotic patients achieving an SVR and 95.5% HCV GT1 cirrhotic prior null responders also achieving an SVR.

However, for all the other agents, one or more these disease characteristics considerably affect the SVR data but to differing degrees i.e. the effects are treatment specific. For example, it appears that having compensated cirrhosis leads to a 25% reduction in SVR for PegIFN/RBV (44.4% to 33.3%), compared to telaprevir or simeprevir which show about an 18% (75.4% to 61.9%) to 26% (81.9 to 60.4%) relative reduction in SVR; or compared to boceprevir where being cirrhotic appears to lead to a considerable 52.5% relative reduction in SVR (65.9% to 31.3%). Similarly, for null responders, it appears that there is a dramatic 12-fold reduction in SVR for PegIFN/RBV (91.6% reduction, 44.4% to 3.7%), a 53.8% and 38.6% reduction for

telaprevir (75.4% to 34.8%) and simeprevir (81.9% to 50.3%) respectively; and a 0.2% reduction for AbbVie's 3D (96.8% to 96.6%).

Therefore, AbbVie concludes that unless like-for-like can be compared, or there are considerable treatment specific adjustments made to any analyses, then all NMAs in this disease area should be interpreted with caution.

Table 58: Treatment-specific impact of certain disease characteristics on ability to achieve SVR for different HCV GT1 regimens

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

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

Data for 3D are pooled for the relevant sub-group across all trials.
Data for PegIFN/RBV for naïve and experienced patients from PegIFN/RBV arms of the telaprevir trials ADVANCE (NEJM, Jacobson et al, 2011) and REALIZE (NEJM, Zeuzem et al, 2011), respectively.
Data for telaprevir for naïve patients and experienced patients from ADVANCE (NEJM, Jacobson et al, 2011) and REALIZE (NEJM, Zeuzem et al, 2011), respectively.
Data for boceprevir from SPRINT-2 (NEJM, Poordad et al, 2011).
Data for sofosbuvir from NEUTRINO (NEJM, Lawitz et al, 2013).
Data for simeprevir for naïve patients from QUEST-1 (Lancet, Jacobson et al, 2014) and QUEST-2 (Lancet, Manns et al, 2014), and data for treatment-experienced patients from ATTAIN (Figure 15, page 56 of MS submission to NICE).

6.8 Non-RCT evidence

6.8.1 **If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.**

Not applicable – all trials reported in Sections 6.3 - 6.5.

6.9 Adverse events

6.9.1 **If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.**

The phase III trials were designed to primarily assess clinical efficacy, as such a full systematic review has not been undertaken. However, in each study assessment of safety was an objective and the results are reported in Section 6.9.2 below.

Adverse events were assessed at each study visit. The investigator at each site classified events as mild, moderate, or severe. Data on all adverse events were collected from the start of study drug administration until 30 days after receipt of the last dose. Data on serious adverse events were collected throughout the entire study period.

6.9.2 **Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event.**

Important adverse events for all the completed phase III studies in the AbbVie HCV clinical trial programme (and the two phase II studies included in the supplementary information filed to EMA) are presented in the tables below:

6.9.2.1 SAPPHIRE-I

During the double-blind period, 87.5% of patients receiving 3D + RBV (group A) had an adverse event, as compared with 73.4% of those receiving placebo (group B) (P<0.001; Table 59). Events were mild in most patients. The most common adverse

events were fatigue (in 34.7% of the patients in group A and 28.5% of those in group B) and headache (in 33.0% of the patients in group A and 26.6% of those in group B); the frequency of these events did not differ significantly between the study groups (P>0.05 for both comparisons). Among adverse events that occurred in more than 10% of patients in either group, five occurred in significantly more patients in group A than in group B (see Table 59).[31]

The most frequent chemical abnormality of grade 3 or 4 in group A was a grade 3 elevated total bilirubin level (in 13 of 469 patients [2.8%]); no patient had an elevation of grade 4. Elevations in the bilirubin level involved predominantly indirect bilirubin. In 9 of these 13 patients, the elevation was observed at a single visit. Two of these 13 patients had clinically recognized jaundice. All elevated bilirubin levels improved or resolved without discontinuation of the study drug. [31]

Table 59: Adverse events and chemical and haematological abnormalities of Grade 3 or 4 during the double-blind treatment period of SAPPHIRE-I

Event	Group A: 3D + RBV N=473	Group B: Placebo N=158
Any adverse event, n (%)	414 (87.5) †	116 (73.4)
Any adverse event leading to discontinuation of study drug, n (%) ‡	3 (0.6)	1 (0.6)
Any serious adverse event, n (%) §	10 (2.1)	0
Common adverse event, n (%)		
Fatigue	164 (34.7)	45 (28.5)
Headache	156 (33.0)	42 (26.6)
Nausea	112 (23.7)†	21 (13.3)
Pruritus	80 (16.9)†	6 (3.8)
Insomnia	66 (14.0)†	12 (7.6)
Diarrhoea	65 (13.7)†	11 (7.0)
Asthenia	57 (12.1)†	6 (3.8)
Rash	51 (10.8)	9 (5.7)
Grade 3 or 4 chemical or haematological abnormality, n/N (%) ¥		
Alanine aminotransferase	4/469 (0.9)	7/158 (4.4)†
Aspartate aminotransferase	3/469 (0.6)	3/158 (1.9)
Alkaline phosphatase	0	0
Total bilirubin ǁ	13/469 (2.8)†	0
Haemoglobin	0	0

Source: Feld et al. [31]

* The common adverse events listed here are events that occurred in more than 10% of patients in either group during treatment. Events occurring in more than 5% of patients of any group are shown in Table S5 in the Supplementary Appendix of the publication.

† P<0.05.

‡ Adverse events leading to treatment discontinuation in group A were lobar pneumonia in one patient, acute respiratory failure and hypoxemia in one, and abdominal pain, sinus tachycardia, diarrhoea, chills, vomiting, nausea, and ventricular extrasystoles in one. In group B, syncope led to treatment discontinuation in one patient.

§ Serious adverse events were appendicitis, lobar pneumonia, cholecystitis, and lumbar vertebral fracture (caused by a vehicle accident), occurring in one patient each; aortic stenosis and postoperative wound infection in one; overdose and encephalopathy in one; mediastinal mass and non–small-cell lung cancer in one; acute respiratory failure and hypoxemia in one; abdominal pain, sinus tachycardia, diarrhea, chills, vomiting, nausea, and ventricular extrasystoles in one; and anemia and noncardiac chest pain in one.

¥ Data on alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and hemoglobin levels were missing for four patients in group A. An aminotransferase (alanine or aspartate) level of grade 3 was defined as a level that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as a level that was more

than 20 times the upper limit of the normal range. An alkaline phosphatase level of grade 3 was defined as a level that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as a level that was more than 20 times the upper limit of the normal range. A total bilirubin level of grade 3 was defined as a level that was more than 3 to 10 times the upper limit of the normal range, and grade 4 as a level that was more than 10 times the upper limit of the normal range. A haemoglobin level of grade 3 was defined as a level that was less than 8.0 to 6.5 g per decilitre, and grade 4 as a level that was less than 6.5 g per decilitre. The numbers of patients with a reduced haemoglobin level of grade 1 or 2 are provided in Table S7 in the Supplementary Appendix of the publication.
‖ Total bilirubin was predominantly indirect bilirubin.

In group A, 4 of 469 patients (0.9%) had an elevated alanine aminotransferase level of grade 3 or 4. In these 4 patients, the alanine aminotransferase level declined with ongoing treatment and was either within the normal range or at grade 1 at the first post-treatment visit. One of these 4 patients had an associated grade 2 elevation in the total bilirubin level (predominantly indirect bilirubin), which declined to within the normal range at the first post-treatment visit. All these patients had a SV12. [31]

Grade 1 reductions in the haemoglobin level (ranging from below the lower limit of the normal range to 10.0 g per decilitre) occurred in 47.5% of patients in group A and 2.5% of those in group B. Grade 2 reductions (<10.0 to 8.0 g per decilitre) occurred in 5.8% of patients in group A and in no patients in group B. There were no haemoglobin reductions of grade 3 or 4 (<8.0 g per decilitre) in either study group. The ribavirin dose was modified owing to adverse events in 5.5% of the patients in group A. No patient discontinued the study treatment owing to anaemia. One patient received erythropoietin. No patient received a transfusion. [31]

6.9.2.2 SAPPHIRE-II

During the double-blind treatment period, 91.2% of patients receiving 3D + RBV and 82.5% of patients receiving placebo had an adverse event. In both groups, the two most common adverse events were headache (in 36.4% of patients in the active-regimen group and in 35.1% of those in the placebo group, P = 0.90) and fatigue (33.3% and 22.7%, respectively; P = 0.06) (see Table 60). [32]

Among adverse events occurring in more than 10% of patients in either group, only pruritus had a higher frequency in the active-regimen group than in the placebo group (13.8% vs. 5.2%, P = 0.03). Among adverse events occurring in less than 10% of patients in both groups, those with a higher frequency in the active-regimen group were anaemia (P = 0.01), a decrease in haemoglobin level (P = 0.04), and vomiting (P = 0.006), and those with a higher frequency in the placebo group were constipation (P = 0.02), erythema (P = 0.05), neck pain (P = 0.05), and neutropenia (P = 0.01). [32]

There were no moderate or severe adverse events that occurred more frequently with the active regimen than with placebo (P>0.10 for all comparisons). Six patients in the active-regimen group (2.0%) and one patient in the placebo group (1.0%) had at least one serious adverse event. Three patients in the active-regimen group (1.0%) and no patients in the placebo group discontinued the study drug owing to adverse events. Discontinuation was due to elevated aminotransferase levels (grade 3), diarrhoea, and acute renal failure in one patient each. The case of acute renal failure was a serious adverse event; however, the site investigator deemed this event to be unrelated to direct acting antiviral treatment. [32]

Table 60: Adverse events and chemical and haematological abnormalities of Grade 3 or 4 during the double-blind treatment period of SAPPHIRE-II [32]

Event	Group A: 3D + RBV N=297	Group B: Placebo N=97
Any adverse event, n (%)*	271 (91.2)	80 (82.5)
Any adverse event leading to discontinuation of study drug, n (%)†	3 (1.0)	0
Any serious adverse event, n (%)‡	6 (2.0)	1 (1.0)
Common adverse event, n (%)§		
Headache	108 (36.4)	34 (35.1)
Fatigue	99 (33.3)	22 (22.7)
Nausea	60 (20.2)	17 (17.5)
Asthenia	47 (15.8)	11 (11.3)
Insomnia	42 (14.1)	7 (7.2)
Pruritus*	41 (13.8)	5 (5.2)
Diarrhoea	39 (13.1)	12 (12.4)
Dyspnea	37 (12.5)	10 (10.3)
Cough	32 (10.8)	5 (5.2)
Myalgia	23 (7.7)	10 (10.3)
Grade 3 or 4 chemical or haematological abnormality, n/N (%) ¥		
Alanine aminotransferase	5/296 (1.7)	3/96 (3.1)
Aspartate aminotransferase	3/296 (1.0)	1/96 (1.0)
Alkaline phosphatase	0	0
Creatinine	2/297 (0.7)	0
Total bilirubin	7/296 (2.4)	0
Haemoglobin	1/296 (0.3)	0

* For comparisons between groups, a P value of less than 0.05 was considered to indicate statistical significance. The frequency of any adverse event was significantly greater in the active-regimen group than in the placebo group (P = 0.02), as was the frequency of pruritus (P = 0.03). Fatigue and insomnia were more frequent in the active-regimen group than in the placebo group, but these differences did not reach statistical significance (P = 0.06 and P = 0.08, respectively). P values were greater than 0.10 for all other comparisons between groups.

† Adverse events leading to study-drug discontinuation were elevated aminotransferase levels, diarrhoea, and acute renal failure (in one patient each).

‡ Serious adverse events that occurred in patients in the active-regimen group were chronic obstructive pulmonary disease, acute transient stroke (cerebrovascular accident), pneumonia, acute renal failure, and intestinal obstruction (in one patient each) and dizziness, nausea, vomiting, and bradycardia in one patient. Atrial fibrillation occurred in one patient in the placebo group.

§ Common adverse events were those that occurred in more than 10% of patients in either group during study treatment.

¥ An alanine aminotransferase level of grade 3 was defined as a level that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as more than 20 times the upper limit of the normal range. An aspartate aminotransferase level of grade 3 was defined as a level that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as a level that was more than 20 times the upper limit of the normal range. An alkaline phosphatase level of grade 3 was defined as a level that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as a level that was more than 20 times the upper limit of the normal range. A creatinine level of grade 3 was defined as a level of at least 2.1 to 2.5 mg per decilitre (186 to 221 µmol per litre), and grade 4 as a level that was more than 2.5 mg per decilitre. A total bilirubin level of grade 3 was defined as a level that was more than 3 to 10 times the upper limit of the normal range, and grade 4 as a level that was more than 10

times the upper limit of the normal range. A haemoglobin level of grade 3 was defined as a level of 6.5 to less than 8.0 g per decilitre, and grade 4 as a level that was less than 6.5 g per decilitre.

Abnormalities in laboratory values of grade 3 or 4 that occurred during the double-blind period are shown in Table 60. The most common abnormality of grade 3 or 4 in patients in the active-regimen group was an elevated total bilirubin level, occurring in seven patients (2.4%) (maximum total bilirubin level, 173 µmol per litre [10.1 mg per decilitre]); in six of the patients, these elevations were classified as grade 3. None of these patients had concomitant grade 3 or 4 elevations in the alanine aminotransferase or aspartate aminotransferase level. Elevations in the total bilirubin level were predominantly due to indirect bilirubin and resolved in all patients by post-treatment week 4. Four patients with hyperbilirubinaemia of grade 3 or 4 had jaundice or ocular icterus. No patient discontinued treatment owing to hyperbilirubinaemia. [32]

During the double-blind period, elevations in the alanine aminotransferase level of grade 3 or 4 occurred in 1.7% of patients receiving 3D + RBV and in 3.1% of patients receiving placebo. Elevations in the aspartate aminotransferase level of grade 3 or 4 occurred in 1.0% of patients in each group. During the double-blind period, abnormalities in the haemoglobin value of grade 1 (below the lower limit of the normal range to 10.0 g per decilitre) and grade 2 (8 to <10.0 g per decilitre) occurred in 52.0% and 4.7% of patients in the active-regimen group, respectively. One patient in the active-regimen group (0.3%) had a haemoglobin value of grade 3 (6.5 to <8.0 g per decilitre). No patient had a haemoglobin value of grade 4 (<6.5 g per decilitre). No patient discontinued the study drug owing to anaemia. In 6.4% of patients in the active-regimen group, the ribavirin dose was modified owing to adverse events. No patient received erythropoietin or a transfusion. There were no deaths from any cause in the active-regimen group or the placebo group. [32]

6.6.2.3 TURQUOISE-II

Adverse events were common in both groups, although few occurred more commonly in the 24-week group than in the 12-week group (Table 61). Two percent of patients in either group discontinued the study drug owing to an adverse event. No specific adverse event led to premature discontinuation by more than one patient, and no pattern in the types of adverse events leading to discontinuation was observed. [33]

Table 61: Adverse events and chemical and haematological abnormalities of Grade 3 or 4 in the 12 and 24 week groups from TURQUOISE-II

Event	12 Week 3D + RBV N=208	24 Week 3D + RBV N=172
Any adverse event, n (%)	191 (91.8)	156 (90.7)
Any adverse event leading to discontinuation of study drug, n (%)*	4 (1.9)	4 (2.3)
Any serious adverse event, n (%)†	13 (6.2)	8 (4.7)
Common adverse event, n (%)‡		
Fatigue	68 (32.7)	80 (46.5) §
Headache	58 (27.9)	53 (30.8)
Nausea	37 (17.8)	35 (20.3)
Pruritus	38 (18.3)	33 (19.2)
Insomnia	32 (15.4)	31 (18.0)
Diarrhoea	30 (14.4)	29 (16.9)

Asthenia	29 (13.9)	22 (12.8)
Rash	23 (11.1)	25 (14.5)
Irritability	15 (7.2)	21 (12.2)
Anaemia	16 (7.7)	18 (10.5)
Dyspnoea	12 (5.8)	21 (12.2) ¥
Death	1 (0.5)	0
Grade 3 or 4 chemical or haematological abnormality, n/N (%) ‖		
Alanine aminotransferase	6 (2.9)	0 ¥
Aspartate aminotransferase	1 (0.5)	0
Alkaline phosphatase	0	0
Total bilirubin	28 (13.5)	9 (5.2) §
Haemoglobin	3 (1.5)	1 (0.6)

* Adverse events leading to the discontinuation of treatment are listed in Table S5 in the Supplementary Appendix.
† Serious adverse events that occurred during the treatment period are listed in Table S6 in the Supplementary Appendix of the publication.

‡ Common adverse events were those that occurred in more than 10% of patients in either group during the treatment period.
§ P<0.01 by Fisher's exact test. ¥ P<0.05 by Fisher's exact test.

‖ The abnormalities listed here reflect post-baseline laboratory values, regardless of baseline values. For alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, a level of grade 3 was defined as a value that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as a value that was more than 20 times the upper limit of the normal range. A total bilirubin level of grade 3 was defined as a value that was more than 3 to 10 times the upper limit of the normal range, and grade 4 as a value that was more than 10 times the upper limit of the normal range. For haemoglobin, a level of grade 1 was defined as 10 g per decilitre to less than the lower limit of the normal range, grade 2 as 8 to less than 10 g per decilitre, grade 3 as 6.5 to less than 8 g per decilitre, and grade 4 as less than 6.5 g per decilitre.

The most frequent grade 3 or 4 laboratory abnormalities observed during the treatment period were elevations in total bilirubin levels (in 37 of 380 patients [9.7%]), which predominantly reflected elevated indirect bilirubin values; patients with such elevations did not have concomitant abnormalities in aminotransferase levels of grade 3 or 4. No grade 4 elevations in the total bilirubin level (i.e., >10 times the upper limit of the normal range) were observed. Peak values generally occurred after week 1 or 2 of treatment and declined to baseline levels by the end of the treatment period. Six patients (1.6%) had clinical jaundice, and 2 patients reported scleral icterus. No patient discontinued treatment owing to hyperbilirubinaemia. [33]

Six patients (1.6%) had post-baseline elevations in the alanine aminotransferase level of at least grade 3 during treatment or within 30 days after the end of treatment. Four of these patients completed the study treatment, with normal or grade 1 alanine aminotransferase levels in the post-treatment period; all four had a sustained virologic response by post-treatment week 12. In one of the two patients who prematurely discontinued the study treatment, the elevated alanine aminotransferase level was due to acute hepatitis; in the other patient, the elevation occurred after discontinuation of the study drug. A total of 15 patients in the 12-week group (7.2%) and 19 patients in the 24-week group (11.0%) had a haemoglobin value of grade 2 or higher during the treatment period. In total, 34 patients required a reduction in the ribavirin dose because of anaemia-related adverse events, and all 34 had a sustained virologic response at post-treatment week 12. [33]

One patient had severe lactic acidosis in the context of metformin use and a subsequent ischemic liver injury requiring liver transplantation. Pathological examination of the liver revealed advanced cirrhosis with recent coagulative necrosis of most of the cirrhotic nodules, findings that are characteristic of severe ischemic or hypoxic injury. There was no evidence of diffuse microvesicular steatosis (characteristic of mitochondrial toxic effects) or drug-induced liver injury. The patient died from complications after liver transplantation, including multi-organ failure and septic shock that began 80 days after the last dose of the study drug. [33]

6.6.2.4 PEARL-II

Treatment-emergent AEs (TEAE) were experienced by 79.1% of patients in group 1 and by 77.9% of patients in group 2. Most TEAEs were mild, with the most commonly reported events in group 1 and group 2 being fatigue (31.9% vs 15.8%; P=0.015), headache (24.2% vs 23.2%; P=NS), and nausea (20.9% vs 6.3%; P=0.005), respectively (Table 62). Patients in group 1 also experienced statistically significantly more events of insomnia, anaemia, rash, and increased blood bilirubin levels, all known to be associated with RBV use; no patient discontinued study drug because of these events.[34]

Table 62: Treatment-emergent adverse events from PEARL-II

Event	3D + RBV N=91	3D N=95
TEAE, n (%)	72 (79.1)	74 (77.9)
TEAE leading to discontinuation of study drug, n (%)	2 (2.2)	0
Any serious TEAE, n (%)	2 (2.2)	2 (2.1)
Common TEAEs [a]		
Fatigue ¥	29 (31.9)	15 (15.8)
Headache	22 (24.2)	22 (23.2)
Nausea *	19 (20.9)	6 (6.3)
Insomnia*	13 (14.3)	3 (3.2)
Pruritus	13 (14.3)	8 (8.4)
Diarrhoea	12 (13.2)	12 (12.6)
Asthenia	11 (12.1)	7 (7.4)
Anaemia *	10 (11.0)	0
Rash ¥	8 (8.8)	1 (1.1)
Chemical or haematological abnormalities of interest, n/N (%)		
Alanine aminotransferase >5x ULN	0	0
Aspartate aminotransferase >5x ULN	0	1 (1.1)
Total bilirubin level > 3 x ULN *	8 (8.8)	0
Haemoglobin < LLN at end of treatment *	37 (42.0)	5 (5.5)

[a] Investigator-reported TEAEs present in > 10% of either treatment group or with a statistically significant difference between treatment groups.
[b] N = 88 and 91 for group 1 and group 2, respectively, using the intent-to-treat genotype 1b efficacy population.
* P<0.01 by Fisher's exact test. ¥ P<0.05 by Fisher's exact test.

Overall, 2 (1.1%) patients discontinued treatment because of AEs, both in the 3D + RBV group. One patient experienced 2 serious AEs of pancreatitis that were considered by the investigator not to be study drug–related. This patient had increased amylase levels on day 1 before receiving study drug; on day 11, the patient reported abdominal pain and was hospitalised on day 13, at which point study drugs were discontinued. The patient experienced another mild episode of

pancreatitis on day 31 that resolved by day 36. This patient had an HCV-RNA level of 28 IU/mL on day 8. Resistance analysis performed on baseline and post-treatment samples showed no NS3 or NS5B resistance-associated variants present at baseline. The NS5A R30Q variant was present at baseline, and R30Q and Y93H were present at post-treatment week 12. [34]

Another patient reported anxiety, tachycardia, fever, and dyspnea on day 36 that led to study discontinuation; HCV-RNA level on day 32 before discontinuation was less than 15 IU/mL. This patient had no resistance-associated variants in NS3 or NS5A at baseline; NS5B variants C316N and S556G were present at baseline and post-treatment week 4. Excluding the event of pancreatitis, 3 other serious TEAEs (cellulitis, nephrolithiasis, and osteoarthritis) were reported; none were judged to be study drug–related or led to study drug discontinuation. [34]

Haemoglobin levels less than the lower limit of normal at the end of treatment was experienced more often by patients in the 3D + RBV group compared with patients receiving 3D alone (42.0% vs 5.5%, respectively; P < .001). Clinically significant grade 2 haemoglobin level declines to less than 10 g/dL at the end of treatment occurred in 2 (1.1%) patients, both in the 3D + RBV group. No patient required a blood transfusion or erythropoietin. [34]

Increases in total bilirubin level greater than 2 times the upper limit of normal (ULN) were reported in 15.4% of patients receiving 3D + RBV (group 1) and in 1.1% of patients receiving 3D alone (group 2, P < .001), with 8.8% of patients in group 1 and 0% in group 2 reporting greater than 3 times the ULN. Mean levels of total bilirubin peaked at week 1 (predominantly indirect bilirubin) and were reduced at week 2 in both groups, although levels remained increased throughout the treatment period only in the 3D + RBV group. The mean total bilirubin level at week 1 was 1.6 mg/dL in group 1 and 0.9 mg/dL in group 2; by week 2, the mean levels were reduced to 1.2 and 0.7 mg/dL, respectively. Five (5.5%) patients in group 1 and 2 (2.1%) patients in group 2 reported hyperbilirubinaemia; 3 (3.3%) patients in group 1 reported jaundice. One hyperbilirubinaemia and 1 jaundice event were moderate in severity and the remaining events were judged as mild; none led to study drug discontinuation. Ribavirin dose modification occurred in 5 patients, 3 owing to anaemia, 1 owing to hyperbilirubinaemia, and 1 was dose adjusted owing to a decrease in weight; all achieved SVR12. [34]

The percentage of patients with post-baseline alanine aminotransferase (ALT) levels greater than 3 times the ULN was similarly low for both treatment groups. No patient experienced a post-baseline ALT level greater than 5 times the ULN. One patient in group 2 had an aspartate aminotransferase (AST) level greater than 5 times the ULN at a single study visit, all subsequent values were normal. Twelve weeks of treatment with these regimens normalised liver enzyme levels in almost all patients with high baseline liver enzyme levels: 96.9% (63 of 65) and 100% (66 of 66) of group 1 and group 2 patients, respectively normalised high baseline ATL levels after being treated; AST levels were normalised in 98.4% (60 of 61) and 91.8% (56 of 61) of group 1 and group 2 patients, respectively. Median changes from baseline in aminotransferase values at the final treatment visit were similar when comparing treatment groups (ALT, -35.0 vs -36.0 U/L; AST, -22.0 vs -21.0 U/L for group 1 and group 2, respectively). [34]

6.6.2.5 PEARL-III and PEARL-IV

In both studies, adverse events were more frequently reported in the groups receiving antiviral regimens that contained ribavirin than in the groups that received the ribavirin-free regimen (P = 0.03 in the genotype 1a study and P = 0.003 in the genotype 1b study) (Table 63). The most common adverse events reported in the two studies, headache and fatigue, did not differ significantly in either study between the group that received ribavirin and the group that did not receive it. Among other common adverse events, pruritus, nausea, and insomnia occurred at a higher frequency among patients who received ribavirin than among those who did not in one or both studies. The majority of adverse events in all treatment groups were mild; overall, two patients (both in the genotype 1a study) discontinued the study drugs owing to adverse events. Serious adverse events occurred in eight patients in the genotype 1b study (four who received ribavirin and four who did not) and in four patients in the genotype 1a study (three who received ribavirin and one who did not). All patients with a serious adverse event had a sustained virologic response.[35]

Decreased Haemoglobin Levels

Among the patients in the genotype 1a study who had a haemoglobin level within the normal range at baseline, 42.0% of patients who received the antiviral regimen with ribavirin and 3.9% of patients who received the ribavirin-free regimen had a haemoglobin level below the lower limit of the normal range at the end of treatment (P<0.001). Similarly, in the genotype 1b study, 51.2% of patients who received ribavirin had a low haemoglobin level at the end of treatment, as compared with 3.4% of patients who did not receive ribavirin (P<0.001). A haemoglobin level of less than 10g/dL at any time during treatment occurred in 4.0% of patients with genotype 1a infection who received ribavirin and in 9.0% of patients with genotype 1b infection who received ribavirin but did not occur in any patients who received the ribavirin-free regimen (Table 3). The ribavirin dose was reduced in accordance with the protocol because of a decreased haemoglobin level in 6 patients with genotype 1a infection who received ribavirin (6.0%) and in 16 patients with genotype 1b infection who received ribavirin (7.6%); all these patients had a sustained virologic response. [35]

Other Laboratory Abnormalities

In both studies, the proportions of patients with elevations in the serum level of bilirubin were higher in the groups that received the ribavirin containing regimen than in the groups that received the ribavirin-free regimen. Elevated levels of indirect (unconjugated) bilirubin primarily accounted for the abnormalities in both studies. Mean bilirubin levels peaked 1 week after the start of study-drug treatment and stabilized or normalised thereafter; maximal observed bilirubin levels were 6.5 mg per decilitre in the genotype 1a study and 9.4 mg per decilitre in the genotype 1bstudy. Elevations in the bilirubin level were not associated with elevations in aminotransferase levels. [35]

Table 63: Adverse events and chemical and haematological abnormalities of interest from PEARL-III and PEARL-IV

	PEARL-IV - HCV genotype 1a			PEARL-III HCV genotype 1b		
Event	**3D + RBV N=100**	**3D N=205**	**P value**	**3D + RBV N=210**	**3D N=209**	**P value**
Any adverse event, n (%)	92 (92.0)	169 (82.4)	0.03	168 (80.0)	140 (67.0)	0.003
Any severe adverse event, n (%)†	2 (2.0)	4 (2.0)		2 (1.0)	1 (0.5)	
Any serious adverse event, n (%)‡	3 (3.0)	1 (0.5)		4 (1.9)	4 (1.9)	
Common adverse events, n (%)§						
Headache	25 (25.0)	58 (28.3)		51 (24.3)	49 (23.4)	
Fatigue	46 (46.0)	72 (35.1)		45 (21.4)	48 (23.0)	
Pruritus	10 (10.0)	12 (5.9)		25 (11.9)	11 (5.3)	0.02
Nausea	21 (21.0)	28 (13.7)		23 (11.0)	9 (4.3)	0.02
Insomnia	17 (17.0)	16 (7.8)	0.02	19 (9.0)	7 (3.3)	0.02
Diarrhoea	14 (14.0)	33 (16.1)		9 (4.3)	13 (6.2)	
Chemical or haematological abnormalities of interest, n/N (%)						
Haemoglobin < LLN at end of treatment, n (%) ¥	42/100 (42.0)	8/203 (3.9)	<0.001	106/207 (51.2)	7/205 (3.4)	<0.001
Haemoglobin ≤ 10 g/dL, n (%)	4 (4.0)	0	0.01	19 (9.0)	0	<0.001
Total bilirubin level > 3 x ULN, n (%)	3 (3.0)	1 (0.5)		12 (5.7)	1 (0.5)	0.003
Alanine aminotransferase >5x ULN, n (%)	1 (1.0)	1 (0.5)		2 (1.0)	0	
Aspartate aminotransferase >5x ULN, n	0	0		0	0	
Alkaline phosphatase > 2.5 x ULN, n	0	0		0	0	

Source: Ferenci et al [35]

† A severe adverse event was defined as one that caused considerable interference with the usual activities of the patient and that may have been incapacitating or life-threatening.

‡ A serious adverse event was defined as one that resulted in hospitalization, persistent or clinically significant disability, or death or that was life-threatening or required medical intervention or hospitalization to prevent a serious outcome.

§ All other adverse events occurred in less than 10% of patients in any treatment group.

¥ Patients with a haemoglobin level below the LLN at baseline were not included in the analysis.

6.6.2.6 AVIATOR

A total of eight patients (1%) discontinued study drug therapy owing to adverse events, including six previously untreated patients and two who had not had a response to prior therapy (Table 2). The reasons for discontinuation included affective disorder, homicidal ideation, convulsion, jitteriness, and confusional state. Six of these patients had a sustained virologic response at 24 weeks after treatment, including both patients who had not had a response to prior therapy. Serious adverse events occurred in eight patients (1%) during the study treatment period or the following 30 days (Table 2). One event (arthralgia) was considered by the investigator to be possibly related to a study drug.[36]

Adverse events that occurred during treatment in more than 20% of patients in any group are shown in Table 2. The most common adverse events were fatigue, headache, nausea, and insomnia. The nature and frequency of adverse events were similar across treatment groups. [36]

Laboratory abnormalities of grade 3 or 4 that occurred in more than 1 patient in any group are shown in Table 2. A total of 11 patients (2%) had grade 3 elevations in the bilirubin concentration (predominantly indirect bilirubin), which normalised during or immediately after treatment. No patient had a grade 4 elevation. These elevations were not associated with elevations in aminotransferase levels. A total of 5 patients (1%) had a grade 3 elevation in the alanine aminotransferase level, with a maximum alanine aminotransferase level of 408 U per litre; there were no grade 4 elevations. Alanine aminotransferase levels normalized in each case without interruption of the study drug. Triglyceride values of grade 3 or 4 were observed in 7 patients (1%); in 4 patients, the samples were not obtained while the patient was fasting. Anaemia developed during the treatment period in 5% of previously untreated patients, in 6% of patients who had not had a response to prior therapy, and in 1% of patients who did not receive ribavirin. No grade 3 or 4 decreases in the haemoglobin level were observed. [36]

Table 64: Adverse Events and Chemical and Haematologic Abnormalities of Grade 3 and 4 occurring during the treatment period in AVIATOR [36]

	Treatment naïve patients						Patients without a response to prior therapy		
Event	**Group 1 N=80 8wk 3D + RBV**	**Group 2 N=41 12wk ABT-450/r + ABT-333 + RBV**	**Group 3 N=79 12wk ABT-450/r + ABT-267 + RBV**	**Group 4 N=79 12wk 3D**	**Group 5 N=79 12wk 3D + RBV**	**Group 6 N=80 24wk 3D + RBV**	**Group 7 N=45 12wk ABT-450/r + ABT-267 + RBV**	**Group 8 N=45 12wk 3D + RBV**	**Group 9 N=43 24wk 3D + RBV**
Discontinuation due to adverse event, n (%)†	1 (1)	0	0	0	2 (3)	3 (4)	1 (2)	0	1 (2)
Any serious adverse event, n (%)‡	0	0	2 (3)	2 (3)	1 (1)	1(1)	0	0	2 (5)
Common adverse events, n (%)*									
Fatigue	29 (36)	13 (32)	22 (28)	16 (20)	22 (28)	30 (38)	12 (27)	12 (27)	9 (21)
Headache	28 (35)	13 (32)	23 (29)	15 (19)	21 (27)	29 (36)	15 (33)	13 (29)	14 (33)
Nausea	12 (15)	7 (17)	16 (20)	11 (14)	19 (24)	20 (25)	6 (13)	9 (20)	8 (19)
Insomnia	10 (12)	8 (20)	9 (11)	6 (8)	16 (20)	20 (25)	8 (18)	6 (13)	7 (16)
Diarrhoea	8 (10)	10 (24)	8 (10)	13 (16)	10 (13)	11 (14)	7 (16)	8 (18)	8 (19)
Asthenia	7 (9)	1 (2)	8 (10)	5 (6)	3 (4)	12 (15)	10 (22)	4 (9)	4 (9)
Cough	12 (15)	5 (12)	11 (14)	2 (3)	8 (10)	12 (15)	7 (16)	3 (7)	9 (21)
Chemical or haematological abnormalities of grade 3 or 4, n/N (%)									
High total bilirubin § ¥	0	0	3 (4)	0	4 (5)	0	2 (4)	0	2 (5)
High ALT ¥	0	0	3 (4)	0	1 (1)	0	1 (2)	0	0
High glucose	0	0	2 (3)	0	1 (1)	0	1 (2)	0	1 (2)
Low sodium	0	0	2 (3)	0	1 (1)	1 (1)	0	0	0
High triglycerides	0	0	3 (4)	0	1 (1)	1 (1)	1 (2)	0	1 (2)
Increased white cell count	1 (1)	0	0	2 (3)	1 (1)	0	1 (2)	0	0
Low lymphocyte count	1 (1)	0	0	2 (3)	1 (1)	1 (1)	0	0	0

* Common adverse events listed here are events occurring during the treatment period in more than 20% of patients in any group.

† Adverse events leading to the discontinuation of treatment were decreased creatinine clearance, affective disorder, homicidal ideation, convulsion, cholestatic hepatitis, and anxiety(occurring in one patient each); asthenia, jitteriness, and confusional state occurring in the same patient; and headache, constipation, nausea, diarrhoea, aphthous stomatitis, generalised pruritus, and burning sensation occurring in the same patient.

‡ Serious adverse events that occurred during the treatment period were affective disorder, animal bite, arthralgia, acute cholecystitis, and facial paresis (occurring in one patient each); increased blood creatinine level and bronchitis occurring in the same patient; the cervicobrachial syndrome, neck pain, and osteoarthritis of the spine occurring in the same patient; and lung disorder and pneumonia occurring in the same patient.

§ The measurement was of predominantly indirect bilirubin.

¥ Bilirubin elevations of grade 3 were not concurrent with aminotransferase elevations of grade 3.

6.6.2.7 M14-103

Table 65 summarises adverse events of interest from the phase II, single-arm study M14-103 in HCV GT1-infected patients on stable opioid replacement therapy.[49]

Table 65: Adverse events and chemical and haematological abnormalities from M14-103

Event	3D + RBV N=38
Any adverse event, n (%)	35 (92.1)
Treatment adverse event leading to discontinuation of study drug, n (%)	1 (2.6)
Any severe adverse event, n (%)	3 (7.9)
Common adverse events [a]	
Nausea	19 (50.0)
Fatigue	18 (47.4)
Headache	12 (31.6)
Insomnia	7 (18.4)
Rash	6 (15.8)
Anxiety	5 (13.2)
Arthralgia	5 (13.2)
Anaemia	4 (10.5)
Irritability	4 (10.5)
Vomiting	4 (10.5)
Chemical or haematological abnormalities of grade 3 or 4, n/N (%)	
Alanine aminotransferase >5x ULN	0
Aspartate aminotransferase >5x ULN	0
Total bilirubin level ≥ 2 x ULN	4 (10.5)
Low haemoglobin levels	2 (5.3)

[a] Common adverse events occurred in ≥ 10% of subjects

6.6.2.8 PEARL-I - HCV GT4

Table 66 summarises the safety data reported from PEARL-I in patients with HCV GT4. The data show that the majority of all AEs were mild. Few severe AEs were reported, occurring in 3 out of 135 GT4 subjects. The incidence of serious adverse events (SAEs) was low, reported for only 1 subject treated with 2D in Group 1 (contusion and road traffic accident). The SAE was resolved and was considered not related to study drug by the investigator. No SAEs were reported for subjects treated with 2D + RBV (Groups 4 and 6). No TEAEs resulted in death or study drug discontinuation for any subject.[39]

Haematology results showed small mean decreases in haemoglobin that were greater for 2D + RBV treatment (–20.6 g/L at Final Treatment Visit) than for 2D treatment (–5.3 g/L Final Treatment Visit). The mean decreases were observed within the first 4 weeks of treatment, were not progressive over time, and the values for 2D + RBV treatment returned to near baseline levels within 4 weeks after the end of treatment. Additional parameters of interest are presented in Table 66 below. [39]

Table 66: Adverse events and chemical or haematological abnormalities of interest from PEARL-I in HCV GT4 subjects [39]

	Tx naive		Tx-experienced
Event	**Group 1: 2D N=44**	**Group 4: 2D + RBV N=42**	**Group 6: 2D + RBV N=49**
Any adverse event, n (%)	34 (77.3)	37 (88.1)	43 (87.8)
Any adverse event leading to discontinuation of study drug, n (%)	0	0	0
Any serious adverse event, n (%)	1 (2.3)	0	0
Any severe adverse event, n (%)	1 (2.3)	1 (2.4)	1 (2.0)
Common adverse event, n (%)			
Fatigue	3 (6.8)	5 (11.9)	9 (18.4)
Headache	13 (29.5)	14 (33.3)	14 (28.6)
Nausea	4 (9.1)	7 (16.7)	6 (12.2)
Pruritus	2 (4.5)	1 (2.4)	5 (10.2)
Insomnia	2 (4.5)	4 (9.5)	8 (16.3)
Diarrhoea	2 (4.5)	6 (14.3)	3 (6.1)
Asthenia	11 (25.0)	10 (23.8)	16 (32.7)
Chemical or haematological values of interest, n/N (%)			
Alanine aminotransferase >5 x ULN	0/43 (0)	0/42 (0)	0/49 (0)
Aspartate aminotransferase >5 x ULN	1/43 (2.3)	0/42 (0)	0/49 (0)
Alkaline phosphatase >1. 5 x ULN	0/43 (0)	0/42 (0)	0/49 (0)
Total bilirubin ≥ 2 x ULN	0/43 (0)	1/42 (2.4)	6/49 (12.2)
Haemoglobin < 80g/L	0/43 (0)	1/42 (2.4)	0/49 (0)

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The safety and tolerability of 3D with or without ribavirin has been assessed in over 2,500 subjects with HCV. The data show that 3D co-administered with or without RBV in adults with HCV, including difficult to treat subjects with cirrhosis, or patients with post-liver transplant and those with HIV-co-infection, was well tolerated for up to 24 weeks, as evidenced by the low rate of treatment discontinuation and serious adverse events. ALT and bilirubin elevations were rarely treatment limiting. The regimen without RBV was associated with a lower incidence of treatment-emergent adverse events of nausea, anaemia, insomnia, asthenia, and rash-related adverse events, as well as a lower rate of laboratory abnormalities, including bilirubin elevations and a decrease in haemoglobin levels.

Given the well documented side effects associated with Peg-interferon, the all oral, interferon-free regimen of 3D and 2D represents a significant improvement for HCV patients, which should result in reduced resource use in the NHS and a greater likelihood of achieving an SVR and thus preventing onward transmission of hepatitis C.

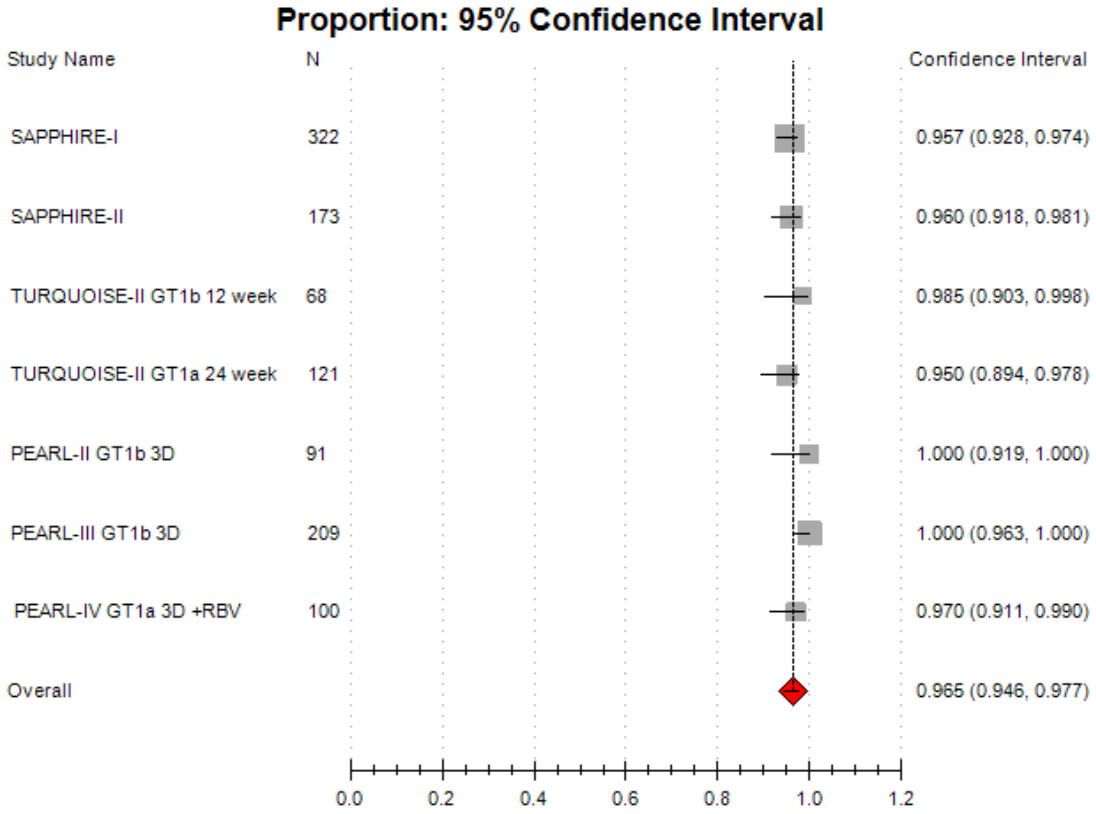
6.10 *Interpretation of clinical evidence*

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

AbbVie's HCV GT1 and GT4 regimens represent one of the first all oral, PegIFN free treatments for people infected with chronic hepatitis C. The safety and efficacy of both 3D and 2D have been studied in an extensive clinical trial programme in over 2,500 chronically infected HCV patients. Treatment goal in HCV is 'cure' – measured by SVR - to prevent onward transmission and progression to fibrosis, cirrhosis, HCC and death.

In HCV GT1, treatment with 3D +/- RBV resulted in consistently high SVR rates across a broad population of patients including treatment naïve and treatment–experienced patients, as well as difficult-to-treat patients such as those with cirrhosis; and in special populations, such as those with HIV co-infection or those who have had a liver transplant or are receiving opioid replacement therapy. Figure 21 summarises the SVR data across the trials for the arms in line with the licence for 3D, showing a pooled SVR of 96.5% for the overall HCV GT1 population.

Figure 21: Summary of SVR rates in HCV GT1 infected patients for the licensed indication of 3D from AbbVie's completed phase III trials



In HCV GT4, treatment with the licensed regimen of 2D resulted in a phenomenal 100% of treatment naïve and 100% treatment-experienced patients achieving SVR12.

The clinical benefits of being able to achieve such high SVR rates with 3D and 2D are twofold: firstly, the likelihood of onward transmission is considerably reduced, and secondly SVR12 results in regression of fibrosis and cirrhosis (i.e. liver function improves) and it is associated with a reduced rate of hepatic decompensation, a reduced risk for HCC and both a reduced rate of liver and non-liver related mortality.[15]

Furthermore, because AbbVie's highly efficacious regimens are completely PegIFN free, patients who are currently ineligible for PegIFN containing regimens will be able to receive 3D for HCV GT1 or 2D if they have HCV GT4. This is a huge clinical benefit, as the only other treatment option to date for these patients has been best supportive care.

In addition to the high probability of achieving SVR with AbbVie's regimens, the clinical evidence shows that there are very few side effects associated with 3D and 2D. Firstly, all the clinical trials collected patient reported outcome data looking at HRQoL – namely, the SF-36, EQ-5D-5L and the HCV-PRO. These data show that there was very little to no impact on HRQoL during treatment with either 3D or 2D as there was no worsening in HRQoL from baseline through to the end of the treatment period.

Secondly, Section 6.9 summarises the adverse events from the HCV clinical trial programme. In the SAPPHIRE trials, which evaluated safety outcomes for 3D + RBV vs placebo, there were no significant differences in the number of serious adverse events between 3D + RBV vs. placebo. Significant differences that were reported for some of the more common adverse events were mostly attributable to the co-administration of RBV. This is evidenced by the adverse event data from PEARL-II, PEARL-II and PEARL-IV which evaluated 3D alone with 3D + RBV, and there were significantly less adverse events for 3D vs. 3D + RBV.

Therefore, because AbbVie's regimens are interferon-free and all oral, they have the additional clinical benefit over existing treatments of a dramatically improved tolerability profile versus existing interferon containing regimens as well as removing the need to self-inject.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

<u>Strengths</u>

There are a large number of strengths with regards to AbbVie's clinical evidence for HCV GT1 and HCV GT4. These strengths are summarised below:

- There is an extensive evidence base specifically in HCV GT1compared to the comparators listed in the decision problem. AbbVie's 3D regimen has been studied in over 2,000 patients with HCV GT1 including sites in the UK. Furthermore, SVR rates are consistently high across a broad population of HCV patients that are reflective of those who will be eligible for treatment in the UK - namely treatment-naïve patients, treatment-experienced patients, those unsuitable IFN based regimens, difficult-to-treat patients such as those with cirrhosis and in special populations, those with HIV co-infection and those who have had a liver transplant.

- AbbVie is the first company to conduct a trial solely in cirrhotic patients, a notoriously difficult-to-treat population. TURQUOISE-II was a large multinational study in 380 treatment naïve or treatment-experienced HCV GT1 patients with compensated cirrhosis. The overall SVR12 in treatment naïve and treatment-experienced patients receiving the licensed dose of 3D was 96.3%. This is considerably higher than any SVR data in cirrhotic patients reported for the comparator agents listed in the final scope; where e in treatment naïve cirrhotic patients only the SVR rates for PegIFN/RBV, TPV + PegIFN/RBV, BOC + PegIFN/RBV, simeprevir + PegIFN/RBV and sofosbuvir + PegIFN/RBV were 33.3%, 61.9%, 31.3%, 60.4% and 80.8% respectively (see Table 58).

- In addition to the cirrhotic trial TURQUOISE-II, AbbVie conducted trials such as the SAPPHIRE or PEARL trials where specific patient populations of interest were the focus of the trials. For example, the PEARL trials focused on specific sub-genotypes in HVC GT1 and examined the safety and efficacy of AbbVie's 3D regimen with or without co-administered ribavirin. Importantly in PEARL-II and PEARL-III, administration of 3D alone resulted in both HCV GT1b-infected treatment naïve and treatment-experienced patients achieving 100% SVR12. SAPPHIRE-I focused specifically on treatment naïve HCV GT1 Patients, whereas SAPPHIRE-II focused on treatment-experienced subjects. Furthermore, all of AbbVie's treatment-experienced trials capped recruitment of partial responders and relapsers to previous PegIFN/RBV treatment to ensure that a large proportion of the more-difficult to treat previous null-responder patient population were included.

- The safety and efficacy of 3D has also been studied in special populations: HCV infected patients with HIV co-infection; post-transplant patients; and those receiving opioid replacement therapy. Whilst the trials in HIV co-infection and post-transplant have not yet completed, interim results from TURQUOISE-I (HIV co-infection) and CORAL-I (post-transplant) demonstrate that SVR12 rates are consistent with SVR12 rates reported in the phase 3 trials of HCV mono-infected subjects. In TURQUOISE-I, 100% subjects with genotype 1b infection and 91.1% subjects with genotype 1a infection achieved SVR12. In CORAL-I, 100% subjects with genotype 1b infection and 96.6% subjects with genotype 1a infection achieved SVR12. In the opioid replacement study 97.4% patients achieved SVR12. These data show that consistently high SVR rates are achievable with 3D.

- In comparison to other directly acting anti-viral agents, AbbVie conducted a relatively large study in both treatment naïve and treatment experienced HCV GT4 infected subjects (n=135). Furthermore, as mentioned in Section 6.10.1, 100% SVR rates were achieved for both treatment naïve and treatment experienced patients receiving 2D + RBV. Therefore, there is a great deal more certainty that patients with HCV GT4 in the UK will achieve SVR if they receive 2D + RBV compared to other agents.

<u>Limitations</u>

There are a few limitations associated with the clinical evidence base discussed below:

- Whilst AbbVie's HCV GT1 clinical trial programme has been conducted in over 2,000 subjects and the majority of the trials were double-blind RCTs, they were designed and powered to detect the inferiority and subsequent superiority of 3D

vs. historical telaprevir + PegIFN/RBV SVR data, where the randomised arms are for example 3D with or without ribavirin, or 12 vs 24 weeks of treatment. Therefore, there are no reference or comparator arms in AbbVie's trials, not even placebo. This could be considered a limitation, and was one of the reasons an indirect comparison or NMA could not be performed (see Section 6.7). However, given that 3D is an all oral and completely interferon free regimen and therefore constitutes a paradigm shift in treatment, it was agreed with the regulatory bodies that an analysis powered to detect non-inferiority and subsequent superiority vs. historical telaprevir data would suffice. For all of AbbVie's trials, 3D easily demonstrated superiority vs. telaprevir - a comparator in this appraisal. In addition, placebo controlled trials were used only to assess adverse events as the expectation of SVR for placebo is 0% and it was considered inappropriate to make patients wait for SVR12 before switching them to active therapy.

- AbbVie's clinical trial programme comprises a mixture of double-blind and open-label studies (e.g. PEARL-II and TURQUOISE-II were open label, but the SAPPHIRE studies and PEARL-III and IV were double-blinded). One of the limitations of open-label studies is the potential for bias if a patient knows they are receiving treatment, it is particularly important for outcome measures that are quite subjective or that have a large patient reported component to them. In most trials that use a subjective outcome measure, there is quite a high placebo response, which is where blinding becomes very important in determining the true effect of a given treatment. However, SVR is an entirely objective outcome measure and is based on the plasma levels of HCV RNA after treatment. This is evidenced by the fact that trials in HCV that have had a true placebo arm have shown 0% SVR, there is no spontaneous cure.[50] SVR is not susceptible to the usual biases associated with outcomes that include a PRO component that treatment knowledge could impact. This is supported by the fact that SVR rates across AbbVie's HCV GT1 clinical trial programme of both double-blinded and open-label studies were very similar and consistently high at around 95%. Therefore, AbbVie considers that the open-label studies are equally as valid as the double-blind trials, and because SVR is an entirely objective measure not prone to bias, the results from these studies are equally as valid as those reported from the double-blind studies.

- The licence for AbbVie's HCV GT4 regimen includes treatment of patients with compensated cirrhosis. However, the GT4 study PEARL-I was only conducted in treatment naïve and treatment-experienced non-cirrhotic subjects. Whilst there are presently no data available on the treatment of patients with genotype 4 and cirrhosis, EMA noted that the in vitro EC50 for GT1b and GT4 from PEARL-I is similar for both paritaprevir and ombitasvir. Furthermore, based on the pharmacodynamics data EMA concluded that the barrier to resistance may be roughly similar for both drugs and (sub)genotypes. Therefore, given that 2D was highly effective when given for 24 weeks to GT1b cirrhotics (data from PEARL-I not shown in the submission), the EMA concluded that an inference of likely similar efficacy of 2D + RBV if given for 24 weeks to GT4 cirrhotics can be made.

  Whilst AbbVie has a licence for use in GT4 cirrhotics, this patient population has not been included in the economic model or Section 7 because there are no data specifically in this group, only data inferred from another genotype. This is in keeping with assumptions AbbVie has had to make for other comparisons where in the absence of data, a comparison could not be carried out.

- This submission has demonstrated that there is a considerable evidence base evaluating the safety and efficacy of AbbVie's HCV regimens, particularly in GT1. However, several important studies are still ongoing which could provide more evidence and add further strength to this submission. For example, the MALACHITE trials are head-to-head randomised, open-label studies evaluating the efficacy and safety of AbbVie's 3D regimen co-administered with RBV vs. telaprevir + PegIFN/RBV in both treatment naïve (MALACHITE I) and treatment experienced (MALACHITE II) patients with HCV GT1. Final data collection for the primary outcome measure is expected December 2014. In addition, whilst interim results have been included here – final data from the HIV co-infection study and the post-transplant study have yet to be collected.

6.10.2 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Over 2,000 subjects with HCV GT1 have been studied in AbbVie's clinical trial programme including patients from the UK. Furthermore, the studies reflect the broad patient population in the real world who will be eligible for treatment - including treatment naïve and experienced patients, patients with cirrhosis, patients on stable opioid replacement therapy, post-transplant patients and patients with HIV co-infection. Therefore, given that special populations and difficult to treat patients were not excluded from AbbVie's HCV clinical programme, the efficacy outcomes seen within the clinical trials are expected to be replicable in real-life clinical practice.

The primary outcome of the trials was sustained virologic response (SVR12), which is an appropriate and accepted outcome in the clinical and regulatory environment. The EASL guidelines state that the primary goal of therapy is to eradicate HCV infection, in other words cure the disease, and SVR acts as the indicator for this (EASL 2014). SVR leads to a regression of fibrosis and cirrhosis (i.e. liver function improves) and has been associated with a reduced rate of hepatic decompensation, a reduced risk for HCC and both a reduced rate of liver and non-liver related mortality.[15] Furthermore, because of the high probability of achieving an SVR seen with 3D and 2D – the pooled analysis from 2,091 HCV GT1 subjects in Section 6.5.3 shows that the average SVR12 rate is 96.4% - the likelihood of onward transmission is considerably reduced, a further substantial benefit to patients in clinical practice and to society by helping to reduce the pool of HCV infection in the UK.

Therefore, through improving cure rates combined with increasing the number of patients eligible for treatment (3D and 2D are interferon-free regimens, and so patients who are currently ineligible for PegIFN containing regimens will be able to receive 3D for HCV GT1 or 2D if they have HCV GT4), AbbVie's HCV regimens have the potential to positively impact on public health via a positive impact on the overall epidemiology of HCV and reducing the long-term burden to the NHS of HCV. Further, it should be noted that the EMA accepted an accelerated regulatory process for 3D and 2D, a designation only granted to those medicines of major public health interest.

6.10.3 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues

relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

AbbVie is not aware of any factors that could influence the external validity of the results observed in the phase III clinical trials to those expected in clinical practice. As already mentioned elsewhere in this submission, the clinical trial programme reflects the broad patient population in the real world who will be eligible for treatment, including substantial proportions of patients with characteristics that have historically been associated with lower rates of response to treatment such as older age, BMI, cirrhosis, a high baseline HCV viral load, black race and a non-CC IL28B genotype.

No eligibility criteria will be needed in clinical practice other than confirmation of being either HCV GT1 or HCV GT4.

Sub-group analyses presented for each trial in Section 6.5 demonstrate that different demographic factors including race, ethnic group, as well as age and gender, did not have an impact on the SVR rates achieved with 3D supporting the fact that no patient selection criteria are required.

The licensed dose of 3D and 2D was used in all the phase III trials – so 100% of the evidence base from the used the dose of either 3D or 2D stated in the SPC. Where the trial populations and the posology in the SPC differ, are around the co-administration of RBV or the treatment duration of 3D (discussed below).

<u>Co-administration of RBV</u>

For HCV GT1b-infected patients without cirrhosis, the licence does not require RBV, i.e. 3D is given alone. Therefore, the data from subjects in SAPPHIRE-I and SAPPHIRE-II who had HCV GT1b infection and received 3D + RBV, and also the 3D + RBV arms of PEARL-II and PEARL-III do not reflect the licence. However, given the size and extent of the clinical trial programme there is still a great deal of evidence supporting the use of 3D alone in patients with HCV GT1b infection, where 100% of subjects achieved SVR12.

<u>Treatment duration</u>

TURQUOISE-II, the trial in patients with compensated cirrhosis, had both 12 and 24 week treatment arms containing a mixture of treatment naïve and treatment-experienced GT1a and GT1b subjects. According to the licence for 3D, only HCV GT1a cirrhotic patients require 24 weeks treatment with 3D. Therefore, the 24 week SVR data for patients with GT1b are not relevant to the population covered by the SPC.

The SVR data from the 12 week treatment arm for GT1a cirrhotics are still relevant though, as some GT1a-infected patients with cirrhosis may receive 12 weeks treatment with 3D + RBV rather than 24 weeks, dependent on certain prognostic factors and clinician judgement, particularly as the SVR rates are still high. For

example, following 12 weeks of treatment with 3D + RBV, 92.2% of treatment naïve GT1a-infected patients with cirrhosis achieved SVR12.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 **Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.**

A systematic literature review was conducted to identify cost-effectiveness studies of pharmacological treatment for people with chronic HCV. A recent systematic literature review undertaken by NICE, and reported by Hartwell et al., explored the same research question. Therefore, the current review was carried out as an update of the NICE review, with the aim to identify studies that have been published since the systematic review by Hartwell et al 2011.

Since the Hartwell 2011[51] study focused on literature published up until 2009, the current review searched the following databases from 1st January 2009 to 2nd April 2014:

- MEDLINE (including MEDLINE In-Process)
- EMBASE
- EconLit
- NHS Economic Evaluation Database (EED)

Appendix 10 provides full details of the clinical keywords and medical subject headings used to search each database. A combined search was conducted to identify cost-effectiveness analyses and cost studies on healthcare resource use and unit costs associated with the management of chronic HCV. The dataset was then used for the two reviews separately.

To be considered eligible for inclusion, studies had to meet pre-defined eligibility criteria developed based on the submission Scope (Table 67).

Table 67: Protocol for systematic review of cost-effectiveness studies

• Objective	• To identify economic evaluations comparing the costs and consequences of treatment alternatives (ABT-450/ritonavir/ABT-267 and ABT-

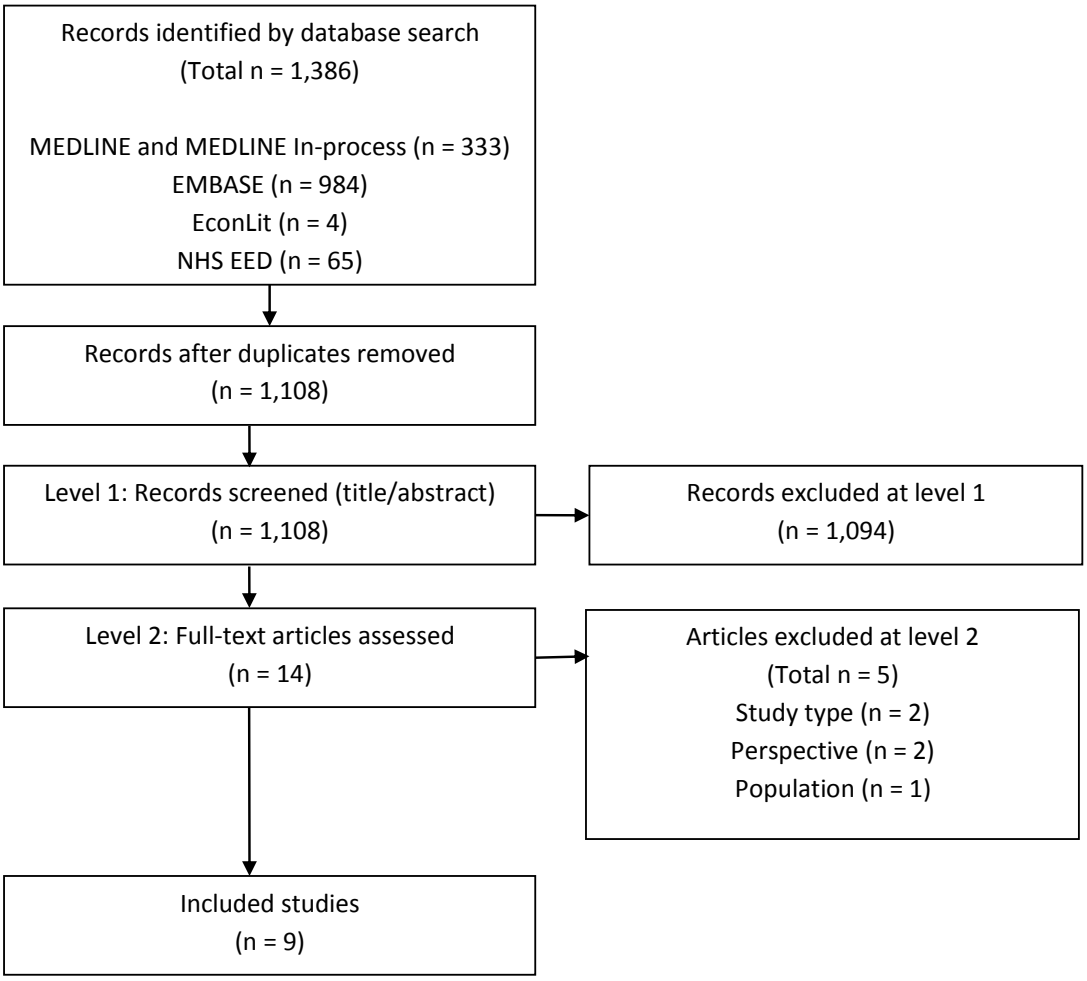
	333 with or without RBV, peg-IFN + RBV, Telaprevir with peg-IFN + RBV, Boceprevir with peg-IFN + RBV) for adults with chronic hepatitis C .
• Disease area	• Chronic Hepatitis C
• Patient population	• Adults with chronic hepatitis C genotype 1 1) who have not been previously treated 2) in whom previous treatment has not resulted in a sustained virological response • The following subgroups will be considered if evidence allows (subgroups are not mutually exclusive): a) Co-infection with HIV b) Response to previous treatment (non-response, partial response, relapsed) • EXCLUDE: • Co-infection with chronic hepatitis B • People with substance dependence or illegal drug users
• Interventions and comparators	• Treatment with any combination of the following: • ABT-450/ritonavir/ABT-267 in combination with ABT-333 • ABT-450/ritonavir/ABT-267 in combination with ABT-333 and ribavirin • Peginterferon-alfa and ribavirin • Telaprevir in combination with peginterferon alfa and ribavirin • Boceprevir in combination with peginterferon alfa and ribavirin
• Study type	• Studies will be included if they report both health service costs and effectiveness, or present a systematic review of such evaluations: • Cost-utility analyses (CUAs) • Cost-effectiveness analyses (CEAs) • Systematic reviews of CUAs/CEAs* • *The bibliographies of systematic reviews will be checked to identify additional CUAs & CEAs. • EXCLUDE: • Non-European country perspective • Within trial economic evaluations (i.e. non-model based evaluations)
• Outcomes/information sought	• Costs o Total costs per comparator o Incremental costs per comparator • Quality adjusted life years o Total QALYs per comparator o Incremental QALYs per comparator • Life years

	○ Total life years per comparator ○ Incremental life years per comparator
• Literature databases	• Using the OVID platform: • MEDLINE • MEDLINE In-process • EMBASE • EconLit • Using the CRD platform: • NHS Economic Evaluations Database
• Language	• English only
• Search dates	• From January 2009 to April 2014

The results of the search were exported to EndNote software and duplicates were removed. Titles and abstracts were reviewed by one reviewer according to the inclusion/exclusion criteria outlined in Table 67: Protocol for systematic review of cost-effectiveness studies. Studies that did not meet inclusion criteria were rejected. Studies that appeared to meet inclusion criteria or that could not be excluded based on title and abstract alone were ordered for full text review. Figure 22 illustrates the study selection process using a PRISMA flow diagram.

Studies that were identified as potentially relevant but did not meet inclusion criteria are summarised in Appendix 10.13.

Figure 22: PRISMA flow diagram of systematic review of cost-effectiveness studies



Description of identified studies

7.1.2 **Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.**

A summary of included cost-effectiveness studies is presented in Table 68.

Table 68: Summary list of other cost-effectiveness evaluations

Study	Country & Perspective	Model summary	Patient population	Comparators	Total Costs	Total QALYs	ICER (cost per QALY)	Uncertainty
Blázquez-Pérez 2013[52]	Spain National Health System	• Markov model based on Townsend 2011[53] • Lifetime horizon • 3 month cycles • Costs and QALYs discounted at 3% • Utilities elicited using EQ-5D	Treatment naïve patients with chronic HCV genotype 1 **Poordad 2011** • 49 years old • 60% male • 89% mild • 6% moderate • 5% cirrhosis **Jacobson 2011** • 49 years old • 60% male • 80% mild • 14% moderate • 6% cirrhosis	Treatment strategies were evaluated separately for each DAA: **Poordad 2011** a) PR[1] b) B/PR IL28B[2] c) B/PR[3] **Jacobson 2011** a) PR[4] b) T/PR IL28B5[E] c) T/PR[6]	2012 Euros **Poordad 2011** a) 18, 93 b) 28,160 c) 33,584 **Jacobson 2011** a) 17,222 b) 30,846 c) 40,120	**Poordad 2011** a) 13.80 b) 14.32 c) 14.34 **Jacobson 2011** a) 13.77 b) 14.30 c) 14.45	Δ€ / ΔQALY **Poordad 2011** a) Baseline b) 18,013 c) 271,200 **Jacobson 2011** a) Baseline b) 25,706 c) 61,827	• Increasing age at beginning of treatment resulted in increased cost and reduced benefit; at ≤60 years the ICER for IL28B therapy was ≤€32,275 and ≤€44,760. At 70 years old, the ICER was doubled. • Reducing the transition probability from hepatitis to cirrhosis from 5.1% to 3.2% increased the ICER for PR to €22,136 and €31,827. • Reducing the effectiveness of each DAA via a 10% SVR relative risk reduction increased the ICER for B/PR and T/PR IL28B strategies to €26,250 and €38,376, respectively, compared with PR. • An increased hazard ratio for all-cause mortality of 2.5 resulted in a reduced ICER for B/PR and T/PR strategies of €8,690 and €12,992 for DT, respectively, compared with PR.

Study	Country & Perspective	Model summary	Patient population	Comparators	Total Costs	Total QALYs	ICER (cost per QALY)	Uncertainty
Camma 2013[54]	Italy National Health Service	• Semi-Markov model • Lifetime horizon • One year cycles • Costs and QALYs discounted at 3% • Utilities elicited using HUI-Mark III	Previously treated patients with chronic HCV genotype 1 • Failed double therapy • 50 years old • 100% male • Liver fibrosis score of F2 Patients entering the model were stratified depending on their treatment history.	1) NT[7] 2) B RGT RR[8] 3) B LI RR[9] 4) T RR[10] 5) T LI RR[11] 6) B GOOD[12] 7) T GOOD[13] 8) B LI PAR[14] 9) T LI PAR[15] 10) T PAR[16] 11) T POOR[17] 12) B POOR[18] 13) T NRT[19] 14) T LI NR[20]	2012 Euros **Prior relapse** 1) 10,640 5) 33,478 2) 33,841 3) 34,477 4) 35,025 **Prior partial response** 1) 10,640 8) 31,816 10) 40,444 9) 40,879 **Prior null response** 1) 10,640 14) 41,059 13) 41,289 **Prior good response** 1) 10,640 6) 34,858 7) 38,878 **Prior poor response** 1) 10,640 12) 31,849 11) 41,059	**Prior relapse** 1) 14.32 5) 19.42 2) 18.45 3) 18.76 4) 19.17 **Prior partial response** 1) 14.32 8) 17.52 10) 17.91 9) 17.63 **Prior null response** 1) 14.32 14) 16.42 13) 16.18 **Prior good response** 1) 14.32 6) 18.97 7) 19.12 **Prior poor response** 1) 14.32 12) 16.48 11)16.42	Δ€ / ΔQALY **Prior relapse** 1) Baseline 5) 4,478 2) Dominated 3) Dominated 4) Dominated **Prior partial response** 1) Baseline 8) 6,616 10) 71,210 9) ED **Prior null response** 1) Baseline 14) 14,485 13) Dominated **Prior good response** 1) Baseline 6) 5,208 7) 26,800 **Prior poor response** 1) Baseline 12) 9,819 11)Dominated	• Note: Method of indirect treatment comparison not stated. **Prior relapse** • At a threshold of €25,000 the T LI RR strategy was cost effective in 98.7% of simulations. • The B LI RR strategy had a 22.1% chance of being both more effective and less expensive than the T LI RR strategy. **Prior partial response** • T PAR and B LI PAR were cost-effective in 75.7% and 86.4% of model simulations, respectively. • The B LI PAR strategy had a 40% chance of being dominant. **Prior null response** • T LI NR was cost-effective in 26.3% of simulations. **Prior good response** • T GOOD and B GOOD were cost-effective in 95.5% and 98.1% of model simulations, respectively, with B GR RGT having a 38% chance of being dominant. **Prior poor response** • T POOR and B POOR were cost-effective in 27% and 55.1% of simulations, respectively.

Study	Country & Perspective	Model summary	Patient population	Comparators	Total Costs	Total QALYs	ICER (cost per QALY)	Uncertainty
Camma 2012[55]	Italy National Health Service	• Semi-Markov model • 20-year horizon • 1 year cycles • Costs and QALYs discounted at 3% per year • Utilities elicited using HUI-Mark III	Treatment naïve patients with chronic HCV genotype 1 • 50 years old • 70 kg • 100% male • F2 Metavir liver fibrosis score	1) PR[21] 2) B/PR RGT[22] 3) B/PR IL28B[23] 4) B/PR RVR GT[24] 5) T/PR RGT[25] 6) T/PR IL28B[26]	2011 Euros 1) 18,337 2) 34,256 3) 31,469 4) 30,542 5) 49,277 6) 39,620	1) 4.58 2) 6.70 3) 7.20 4) 7.21 5) 7.46 6) 7.90	Δ€ / ΔQALY 1) Baseline 2) ED 3) ED 4) ED 5) Dominated 6) 6,414	• Note: Method of indirect treatment comparison not stated. • Probabilistic results not reported as costs per QALY. At a threshold of €25,000 per *life year gained*, T/PR IL28B was cost-effective in 76.6% of model simulations. • In two-way sensitivity analysis, results were sensitive to simultaneous changes in the price of boceprevir and probability of SVR in people with RVR. The model was also sensitive to changes in the price of telaprevir and probability of SVR in people with the IL28B genotype. • In one-way sensitivity analysis, the proportion of patients attaining SVR was the parameter with the greatest impact on model results.

Study	Country & Perspective	Model summary	Patient population	Comparators	Total Costs	Total QALYs	ICER (cost per QALY)	Uncertainty
Cure 2014[56]	England and Wales National Health Service	• Markov model based on Shepherd 2007[57] • Lifetime horizon • 1 year cycles • Costs and QALYs discounted at 3% per year • Utilities elicited using EQ-5D	Previously treated patients with chronic HCV genotype 1 • Age not reported • Sex not reported Prior relapse • 25.4% mild fibrosis • 30.5% moderate fibrosis • 44.1% cirrhosis Prior partial response • 22.4% mild fibrosis • 31.6% moderate fibrosis • 46.1% cirrhosis Prior null response • 13.8% mild fibrosis • 29.4% moderate fibrosis • 56.9% cirrhosis	Patients entering the model were stratified depending on their treatment history: **All patients** 1) PR[28] 2) T/PR[6] **Prior relapse** 1) PR[28] 2) T RR[10] 3) B/PR RGT[27] **Prior partial response** 1) PR[28] 2) T PAR[16] 3) B/PR RGT[27] **Prior null response** 1) PR[28] 2) T NRT[19]	2011 Pounds **All patients** 1) 37,819 2) 44,855 **Prior relapse** 1) 34,977 2) 38,918 3) 52,878 **Prior partial response** 1) 37,891 2) 45,932 3) 53,619 **Prior null response** 1) 43,291 2) 55,705	**All patients** 1) 10.08 2) 11.24 **Prior relapse** 1) 10.48 2) 11.96 3) 11.45 **Prior partial response** 1) 10.11 2) 11.17 3) 11.28 **Prior null response** 1) 9.28 2) 9.87	Δ£ / ΔQALY **All patients** 1) Baseline 2) 6,079 **Prior relapse** 1) Baseline 2) 2,658 3) Dominated **Prior partial response** 1) Baseline 2) 7,593 3) 69,882 **Prior null response** 1) Baseline 2) 20,413	• At a threshold of £20,000 telaprevir triple therapy was cost-effective in 95% of model simulations across all populations compared to standard therapy. • Compared with standard therapy, the cost of telaprevir was less than 10,000 per QALY gained regardless of IL28B genotype. • The model was most sensitive to changes in the cost of telaprevir, discount rates, utilities associated with reaching SVR, utilities associated with entry health states, and the SVR associated with TVR.

Study	Country & Perspective	Model summary	Patient population	Comparators	Total Costs	Total QALYs	ICER (cost per QALY)	Uncertainty
Elbasha 2013[58]	Portugal National Health Service	• Markov model • Lifetime horizon • 1 year cycles • Costs and QALYs discounted at 5% per year • Utilities elicited using EQ-5D	Treatment naïve and experienced patients with chronic HCV genotype 1 • 36.7 years old • 70% male • 98% non-Black Previously untreated • 4.4% F0 • 68.9% F1 • 17.3% F2 • 4.4% F3 • 5.0% F4 Previously treated • 4.8% F0 • 53.3% F1 • 21.1% F2 • 7.7% F3 • 13.1% F4	**Treatment naïve** 1) PR[33] 2) B/PR RGT[22] **Treatment experienced** 1) PR[33] 2) B/PR RGT[27]	2010 Euros **Treatment naïve** 1) 19,988 2) 27,890 **Treatment experienced** 1) 24,272 2) 34,963	**Treatment naïve** 1) 12.59 2) 13.27 **Treatment experienced** 1) 11.84 2) 13.06	Δ€ / ΔQALY **Treatment naïve** 1) Baseline 2) 11,570 **Treatment experienced** 1) Baseline 2) 8,717	• Changing the percentage of the population with cirrhosis has a large effect on the results of the model. The ICER for B/PR for 100% non-cirrhotic and 100% cirrhotic patients was €10,322 and €154,009, respectively. The respective ICERs for previously treated patients were €11,918 and €2,483. • The model was also sensitive to age at the start of treatment. When the age of a previously untreated patient was 25 years old, the ICER decreased to €8,772 per QALY gained and increased to €22,694 per QALY gained at age 55. In previously treated patients, the ICER was €6,830 and €16,397 per QALY gained, respectively. • Treating previous null responders with B/PR was associated with an incremental cost of €9,800 per QALY gained.

Study	Country & Perspective	Model summary	Patient population	Comparators	Total Costs	Total QALYs	ICER (cost per QALY)	Uncertainty
Hartwell 2[59]	England and Wales National Health Service and Personal Social Services	• Markov model based on Shepherd et al., 2007[57] • Lifetime horizon • 1 year cycle • Costs and QALYs discounted at 3.5% per year • Utilities elicited using EQ-5D	People with chronic HCV • 40 years old • 70% male • 46% mild disease • 44% moderate disease • 10% cirrhosis	**Results were reported according to the study from which effectiveness estimates were obtained:** **Liu et al., 2008** 1) PR/48 a-2a[30] 2) PR/24 a-2a[31] **Yu et al., 2008** 1) PR/48 a-2a[30] 2) PR/24 a-2a[31] **Yu et al., 2007** 1) PR/24 a-2a[31] 2) PR/16 a-2a[32] **von Wagner et al., 2005** 1) PR/24 a-2a[31] 2) PR/16 a-2a[32] **Berg et al., 2009** 1) PR/48 a-2b[33] 2) PR/24 a-2b[34]	2008 Pounds **Liu 2008** 1) 14,206 2) 9,399 **Yu 2008** 1) 14,206 2) 8,994 **Yu 2007** 1) 7,834 2) 5,728 **von Wagner et al., 2005** 1) 10,089 2) 6,943 **Berg 2009** 1) 26,169 2) 17,173	**Liu 2008** 1) 15.68 2) 15.54 **Yu 2008** 1) 15.68 2) 15.60 **Yu 2007** 1) 15.64 2) 15.72 **von Wagner et al., 2005** 1) 15.31 2) 15.54 **Berg 2009** 1) 19.74 2) 20.03	Δ£ / ΔQALY **Liu 2008** 1) 34,510 2) Baseline **Yu 2008** 1) 64,880 2) Baseline **Yu 2007** 1) Baseline 2) Dominant **von Wagner et al., 2005** 1) Baseline 2) Dominant **Berg 2009** 1) Baseline 2) Dominant	• For genotype 1 patients, shortened duration therapy was associated with a reduction in total costs of £4,800 to £5,200 and a reduction in QALYs of 0.08 to 0.014 compared with standard duration therapy. • Shortened treatment duration results in fewer patients achieving SVR. Although this is associated with additional costs from disease progression, this is more than offset by the reduced cost of treatment. • Shortened treatment duration also results in fewer adverse events. However, the QALYs gained from this does not offset the QALYs lost as a result of a larger proportion of patients experiencing progressive liver disease.

Study	Country & Perspective	Model summary	Patient population	Comparators	Total Costs	Total QALYs	ICER (cost per QALY)	Uncertainty
Hartwell 2011[51]	England and Wales National Health Service and Personal Social Services	• Markov model • Based on model by Shepherd 2007[57] • Lifetime horizon • 1 year cycle • Costs and QALYs discounted at 3.5% per year • Utilities elicited using EQ-5D	People with chronic HCV who fall into one of three patient groups: Those eligible for shortened treatment duration with peg-IFN • 40 years old • 70% male Those who have been previously treated with PR and are eligible for re-treatment • 45 years old • 70% male Those who are co-infected with HIV Results for genotypes 1&2 and 3&4 reported separately	Eligible for shortened treatment **Liu et al., 2008** 1) PR/48 a-2a[30] 2) PR/24 a-2a[31] **Yu et al., 2008** 1) PR/48 a-2a[30] 2) PR/24 a-2a[31] Eligible for re-treatment following previous non-response 1) BSC[29] 2) PR/72 a-2a[35] Co-infected with HIV 1) BSC[29] 2) PR/48 a-2a[30]	2008 Pounds Eligible for shortened treatment **Liu 2008** 1) 14,206 2) 9,399 **Yu 2008** 1) 14,206 2) 8,994 Eligible for re-treatment following previous non-response 1) 26,221 2) 42,350 Co-infected with HIV 1) 22,201 2) 28,133	Eligible for shortened treatment **Liu 2008** 1) 15.68 2) 15.54 **Yu 2008** 1) 15.68 2) 15.60 Eligible for re-treatment following previous non-response 1) 10.74 2) 11.05 Co-infected with HIV 1) 12.65 2) 13.40	Δ£ / ΔQALY Eligible for shortened treatment **Liu 2008** 1) Baseline 2) 34,510 **Yu 2008** 1) Baseline 2) 64,880 Eligible for re-treatment following previous non-response 1) Baseline 2) 52,587 Co-infected with HIV 1) Baseline 2) 7,941	• At a threshold of £20,000, shortened duration of therapy was cost-effective in 83% of model simulations using efficacy data from Liu 2008 and 100% of simulations using efficacy data from Yu 2008. • Increasing the mean age of patients at the start of the simulation by 15 years results in a doubling of the ICER. • Assumptions regarding the stage of liver disease at the start of treatment also have a large impact on the ICER, with shortened treatment duration being more cost-effective in patients with less severe disease than in those with cirrhosis. • Reducing drug acquisition costs reduced the cost-effectiveness of treatment of shortened duration as it reduces the cost saving between standard and shortened duration while the outcome is unchanged.

Study	Country & Perspective	Model summary	Patient population	Comparators	Total Costs	Total QALYs	ICER (cost per QALY)	Uncertainty
McEwan 2013[60]	England and Wales National Health Service	• Markov model based on the MONARCH model • Lifetime horizon • 1 year cycles • Costs and QALYs discounted at 3.5% per year • Utilities elicited using EQ-5D	Treatment naïve patients with chronic HCV genotype 1 Patients were stratified by liver fibrosis as defined by Metavir stage • 45 years old • 20-year history of HCV • 50% male F0-F2 • 15% NR • 10% DVR • 41% EVR • 34% RVR F3-F4 • 34% NR • 12% DVR • 33% EVR • 21% RVR	All patients received: 1) NT[7] 2) SDT[30] 3) RGT[31]	2011 Pounds **All (F0-F4)** 1) 27,492 2) 29,866 3) 29,762 **F0** 1) 11,517 2) 21,252 3) 21,326 **F1** 1) 19,032 2) 24,465 3) 24,407 **F2** 1) 31,985 2) 30,004 3) 29,718 **F3** 1) 38,310 2) 40,978 3) 41,076 **F4** 1) 45,182 2) 46,069 3) 46,087	**All (F0-F4)** 1) 11.68 2) 13.82 3) 13.88 **F0** 1) 14.51 2) 15.58 3) 15.61 **F1** 1) 13.34 2) 15.08 3) 15.13 **F2** 1) 11.04 2) 13.96 3) 14.05 **F3** 1) 9.41 2) 11.10 3) 11.17 **F4** 1) 7.23 2) 9.46 3) 9.55	Δ£ / ΔQALY **All (F0-F4)** 1) Baseline 2) Dominated 3) Dominant **F0** 1) Baseline 2) 9,098 3) 2,467 **F1** 1) Baseline 2) Dominated 3) Dominant **F2** 1) Baseline 2) Dominated 3) Dominant **F3** 1) Baseline 2) 1,678 3) 1,400 **F4** 1) Baseline 2) 398 3) 200	• Altering the baseline age of the population had a small effect on the incremental results of the model. At age 30 years, RGT is 0.07 QALYs more effective and £71 less expensive (dominant) than SDT. At age 70 years, RGT is 0.02 QALYs more effective and £92 more expensive (ICER £4,600) than SDT. • Changing the percentage of RVR patients with low baseline viral load affects the number of people for whom RGT is relevant and therefore reduces costs. If 20% of patients have low viral load, the cost of RGT is reduced by £2,150. If 60% have low viral load, RGT results in a saving of £3,225. • Threshold analyses were conducted to determine the percentage of patients required to achieve SVR for RGT to be cost-effective in people with RVR at £20,000 per QALY. In patients with RVR: 68% (F0), 72% (F1), 74% (F2), 58% (F3), 60% (F4). In patients with DVR: 53% (F0), 48% (F1), 44% (F2), 25% (F3), 23% (F4). • A discount rate of 0% resulted in a gain of 0.16 QALYs and a saving of £489 (dominant) for RGT compared with SDT. A discount rate of 6% resulted in a gain of 0.04 QALYs and an incremental cost of £13 (ICER £325) for RGT compared with SDT.

Study	Country & Perspective	Model summary	Patient population	Comparators	Total Costs	Total QALYs	ICER (cost per QALY)	Uncertainty
Turnes et al. 2013[61]	Spain National Health System	• Markov model based on Sullivan 2004 (12) • Lifetime horizon • 1 year cycles • Costs and QALYs discounted at 3.5% per year • Utilities elicited using EQ-5D	Treatment naïve patients with chronic HCV 78% G1 & G4 22% G3 & G4 • 48 years old • 70% male • 98% non-Black	All patients received: 1) PR/48 a2a[30] 2) PR/48 a2b[33] Results were reported separately for each genotype.	2010 Euros **G1 & G4** 1) 24,325 2) 24,997 **G2 & G3** 1) 9,104 2) 11,004	 **G1 & G4** 1) 14.238 2) 14.039 **G2 & G3** 1) 15.311 2) 15.085	 **G1 & G4** 1) Dominant 2) Dominated **G2 & G3** 1) Dominant 2) Dominated	• PegIFN a2a + R was found to be the dominant strategy for all genotypes regardless of age at start of treatment, ±10% variation in health state utilities, ±20% variation in health state costs, ±20% variation in probability of transition from CHC to CC and CC to DC, 0% and 6% discount rates and exclusion of patients treated with 1.0ug/Kg per week of pegIFN 2b from the analysis.

Abbreviations: QALY(s), quality-adjusted life years; ICER, incremental cost-effectiveness ratio; EQ-5D, EuroQol 5-Dimensions; DAA, direct acting antiviral; HUI-III, health utilities index mark III; ; ED, extended dominated; HCV, hepatitis C virus; PR, pegylated Interferon plus ribavirin; T/PR, telaprevir plus PR; boceprevir plus PR; IL28B, interleukin 28-B genotype; SDT, standard duration therapy; RGT, response guided therapy; NR, null response; DVR, delayed virological response; EVR, early virological response; RVR, rapid virological response; PSS, personal social services; CC, compensated cirrhosis; DC, decompensated cirrhosis.

Therapy regimens:

1 Standard therapy. Peg-IFN a2b (100ug per week) plus ribavirin (1,000mg per day). Duration not clearly reported.
2 Boceprevir IL28B geotype-guided strategy. Peg-IFN a2b (100ug per week) plus ribavirin (1,000mg per day) administered to IL28B CC genotype patients. Boceprevir triple therapy (see below) administered to IL28B CT and TT patients for 24 or 48 weeks according to HCV-RNA level. Duration not clearly reported.
3 Boceprevir triple therapy. Peg-IFN a2b (100ug per week) plus ribavirin (1,000mg per day) for 4 weeks, Boceprevir (2,400mg per day) plus PR administered to all patients for 44 weeks.
4 Standard therapy. Peg-IFN a2a (180ug per week) plus ribavirin (1,000mg per day). Duration not clearly reported.
5 Telaprevir IL28B geotype-guided strategy. Peg-IFN a2a (180ug per week) plus ribavirin (1,000mg per day) administered to IL28B CC genotype patients. Telaprevir (2,250mg per day) plus PR administered to IL28B CT and TT patients. Duration not clearly reported.
6 Telaprevir triple therapy. Peg-IFN a2a (180ug per week) plus ribavirin (1,000mg per day) plus telaprevir (2,250mg per day) administered to all patients. Duration not clearly reported.
7 No treatment. Patients progress according to the natural history of the disease.
8 Boceprevir lead-in response-guided relapse therapy. Peg-IFN a2b (1.5 ug/kg per week) plus RBV (600 to 1,400 mg per day) for 4 weeks, followed by boceprevir (2,400mg per day) plus PR for 32 weeks. Patients who achieved RVR at weeks 8 and 24 stopped treatment. Those who did not achieve RVR received an additional 12 weeks of PR.

9 Boceprevir lead-in relapse therapy. Peg-IFN a2b (1.5 ug/kg per week) plus RBV (600 to 1,400 mg per day) for 4 weeks, followed by boceprevir (2,400 per day) for 32 weeks in combination with PR, plus an additional 12 weeks of PR.
10 Telaprevir relapse therapy. Peg-IFN a2a (180ug per week) plus ribavirin (1,000 or 1,200 per day) plus telaprevir (2,250 per day) for 12 weeks. Those who achieved RVR received an additional 12 weeks of PR. Those who failed to achieve RVR received an additional 32 weeks of PR.
11 Telaprevir lead-in relapse therapy. Peg-IFN a2a (180ug per week) plus ribavirin (1,000 or 1,200 per day) for 4 weeks, followed by telaprevir (2,250mg per day) in combination with PR for 12 weeks. Those who achieved RVR at week 8 through 16 received another 8 weeks of treatment. Those who did not achieve RVR received another 32 weeks of PR.
12 Boceprevir good responder therapy. Peg-IFN a2b (1.5 ug/kg per week) plus RBV (600 to 1,400 mg per day) for 4 weeks, followed by boceprevir (2,400mg per day) plus PR for 32 weeks HCV RNA drop of >1LOG, then 12 weeks PR.
13 Telaprevir good responder therapy. Peg-IFN a2a (180ug per week) plus ribavirin (1,000 or 1,200 per day) for 4 weeks, followed by 32 weeks of telaprevir plus PR for HCV RNA drop of >1LOG, then 12 weeks PR.
14 Boceprevir lead-in partial responder therapy. Peg-IFN a2b (1.5 ug/kg per week) plus RBV (600 to 1,400 mg per day) for 4 weeks followed by boceprevir (2,400 per day) plus PR for 32 weeks, plus an additional 12 weeks of PR. All treatment discontinued if HCV RNA was detectable at week 12.
15 Telaprevir lead-in partial responder therapy. Peg-IFN a2a (180ug per week) plus ribavirin (1,000 or 1,200 per day) for 4 weeks followed by 12 weeks telaprevir in combination with PR, followed by 32 weeks PR until week 48. All treatment discontinued if HCV RNA decline <2 log10 at week 16.
16 Telaprevir partial-responder therapy. Telaprevir (2,250mg per day) for 12 weeks, in combination with PR for 48 weeks. If HCV RNA decline was <2 log10 at week 12, treatment was discontinued.
17 Telaprevir poor responder therapy. After PR for 4 weeks, patients were defined as poor responsive if they had HCV DNA drop of <1Log and were administered 12 weeks of telaprevir plus PR, followed by 32 weeks PR until week 48. All treatment discontinued if HCV RNA decline <2 log10 at week 16.
18 Boceprevir poor responder therapy. After PR for 4 weeks, patients were defined as poor responsive if they had HCV DNA drop of <1Log and were administered 44 weeks of boceprevir plus PR.
19 Telaprevir null-responder therapy. Telaprevir for 12 weeks in combination with PR for 48 weeks. Treatment was discontinued if HCV RNA decline was < 2Log10 at week 12.
20 Telaprevir lead-in null-responder therapy. PR for 4 weeks, followed by 12 weeks telaprevir plus PR, followed by 32 weeks PR until week 48. All treatment discontinued if HCV RNA decline <2 log10 at week 16.
21 Standard therapy. Peg-IFN a2b (1.5ug/kg per week) plus RBV (600 to 1,400 mg of per day) OR peg-IFN a2a (180ug per week) and RBV (1,000mg per day for body weight < 75kg or 1,200 per day for body weight <75kg) for 48 weeks. Cost of Peg-IFN calculated based on a simple average of a2a and a2b.
22 Boceprevir response-guided therapy. Peg-IFN a2b (1.5ug/kg) plus RBV (600 to 1,400mg per day) for 4 weeks followed by boceprevir (2,400mg per day) plus PR for 24 weeks. For patients with undetectable HCV RNA at 8 through 24 weeks, all treatment was stopped at week 28. For those without extended RVR, B/PR was continued for another 8 weeks, plus an additional 12 weeks of PR.
23 Boceprevir IL28B genotype-guided strategy. Peg-IFN a2b (1.5ug/kg) plus RBV (600 to 1,400mg per day) administered to IL28B CC genotype patients for 48 weeks. Boceprevir (2,400mg per day) plus PR administered to IL28B CT and TT patients as per B/PR RGT strategy (above).
24 Boceprevir RVR-guided strategy. Peg-IFN a2b (1.5ug/kg) plus RBV (600 to 1,400mg per day) for 4 weeks. Patients who achieved RVR treated with PR (duration not reported). Patients who did not achieve RVR treated as per B/PR RGT strategy (above).

25 Telaprevir response-guided therapy. Peg-IFN a2a (180ug per week) plus RBV (1,000 to 1,200 per day) plus telaprevir (2,240mg per day) for 24 or 48 weeks, depending on treatment response at weeks 4 and 12. Treatment was discontinued if HCV RNA was >1,000IU/mL or decline was < 2Log10 at week 12.
26 Telaprevir IL28B genotype-guided strategy. Peg-IFN a2b (1.5ug/kg) plus RBV (600 to 1,400mg per day) administered to IL28B CC genotype patients for 48 weeks. Telaprevir(2,250mg per day) plus PR administered to IL28B CT and TT patients as per T/PR RGT strategy (above). IL28B CC patients who failed achieve SVR were treated with additional 12 weeks of T/PR PR, followed by 36 weeks of PR.
27 Boceprevir response-guided therapy. PR for 4 weeks followed by boceprevir plus PR for 44 weeks. Treatment is stopped at 32 weeks if HCV RNA is undetectable at week 8 to 24.
28 Standard duration therapy. Peg-IFN alfa-2a or alfa-2b plus ribavirin (1,000mg per day) for 48 weeks.
29 Best supportive care. Defined as treatment without any form of interferon therapy.
30 Standard duration therapy (a-2a). Peg-IFN alfa 2a (180ug per week) plus RBV (800, 1,000, or 1,200 per day according to body weight) for 48 weeks.
31 Shortened duration therapy (a-2a). Peg-IFN alfa 2a (180ug per week) plus RBV (800, 1,000, or 1,200 per day according to body weight) for 24 weeks.
32 Shortened duration therapy (a-2a). Peg-IFN alfa 2a (180ug per week) plus RBV (800, 1,000, or 1,200 per day according to body weight) for 16 weeks.
33 Standard duration therapy (a-2b). Peg-IFN alfa 2b (1.5ug/Kg per week) plus RBV (800, 1,000, or 1,200 per day according to body weight) for 48 weeks.
34 Shortened duration therapy (a-2b). Peg-IFN alfa 2b (1.5ug/Kg per week) plus RBV (800, 1,000, or 1,200 per day according to body weight) for 24 weeks.
35 Standard duration therapy (a-2a). Peg-IFN alfa 2a (180ug per week) plus RBV (800, 1,000, or 1,200 per day according to body weight) for 72 weeks.

7.1.3 **Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996) or Philips et al. (2004). For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.**

The quality assessment for the included cost-effectiveness studies is detailed in Table 69 below:

Table 69: Quality assessment of included cost-effectiveness evaluations

	Blázquez-Pérez 2013[52]	**Camma 2013[54]**	**Camma 2012[55]**	**Cure 2014[56]**	**Elbasha 2013[58]**	**Hartwell 2012[59]**	**Hartwell 2011[51]**	**McEwan 2013[60]**	**Turnes 2013[61]**
1. Was the research question stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
4. Was the rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Were the alternatives being compared clearly described?	Partially[1]	Yes (in appendix)	Yes	Partially	Yes	Yes	Yes	Partially	No[1]
6. Was the form of economic evaluation stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was/were the source(s) of the effectiveness estimates used stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Not relevant	Not relevant	Not relevant	Not relevant	Yes	Yes	Yes	Not relevant
10. Were details of the methods of synthesis or meta-analysis given (if based on an overview of a number of effectiveness studies)?	Not relevant	No[2]	No[2]	Partially[3]	Yes	Not relevant	Yes	Not relevant	Yes
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Were the details of the subjects from whom valuations were obtained given?	Partially[4]	No	No	Partially[4]	Partially[4]	Partially[4]	Yes	Partially[4]	No
14. Were productivity changes (if included) reported separately?	Not included	Not included	Not included	Not included	Not included	Not included	Not included	Not included	Not included
15. Was the relevance of productivity changes to the study question discussed?	Yes (broadly)[5]	No	No	No	Yes (broadly)[5]	No	No	No	No
16. Were quantities of resources reported separately from their unit cost?	Partially (for some items)[6]	Partially (for some items)[6]	Partially (for some items)[6]	Partially (for some items) [6]	Partially (for some items)[6]	Partially (for some items)[6]	Partially (for some items)[6]	Partially (for some items)[6]	Partially (for some items)[6]
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Partially	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18. Were currency and price data recorded?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	Not relevant	No	No	Yes	No	Yes	Yes	Yes	No
20. Were details of any model used	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

given?									
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Partially	No	No	Yes	No	Yes	Yes	No
22. Was the time horizon of cost and benefits stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23. Was the discount rate stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
24. Was the choice of rate justified?	Yes	No	No	No	No	No	Yes	No	Yes
25. Was an explanation given if cost or benefits were not discounted?	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Yes	Not relevant	Not relevant
27. Was the approach to sensitivity analysis described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
28. Was the choice of variables for sensitivity analysis justified?	Yes	Yes	No	No	No	Yes	Yes	No	No
29. Were the ranges over which the parameters were varied stated?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
30. Were relevant alternatives compared (That is, were appropriate comparisons made when conducting the incremental analysis)	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
31. Was an incremental analysis reported?	No	No	No	Yes	Yes	Yes	Yes	No	Yes
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	Yes	Yes	Partially	Yes	Yes (in appendix)	Yes	Partially	Yes
33. Was the answer to the study question given?	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

35. Were conclusions accompanied by the appropriate caveats?	Yes	Partially	Partially	Yes	Yes	Yes	Yes	Yes	No
36. Were generalizability issues addressed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

1 Duration of therapy for each strategy not clearly reported.
2 Method of indirect treatment comparison not stated. The proportion of patients achieving SVR appear to have been derived directly from respective clinical studies and applied to the baseline transition probability without adjustment.
3 Meta-analysis on which efficacy estimates were based was cited but not further details provided.
4 Study population (e.g. people with HCV) was reported but no further details were provided.
5 The omission of indirect costs and likely influence on the outcome of the analysis was mentioned in the discussion.
6 Unit costs and resource use reported separately for drug costs but not health state costs, adverse event costs or monitoring costs.

7.2 De novo analysis

Patients

7.2.1 **What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.**

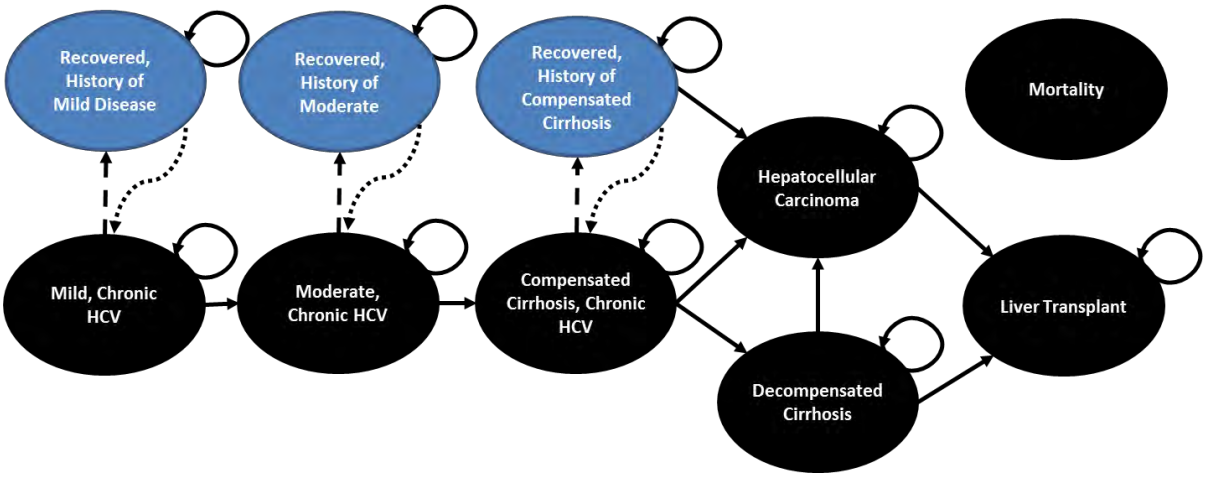
The submission includes de novo economic analyses of patients infected with chronic genotype 1 hepatitis C (HCV) patients for treatment with the AbbVie Regimen. We analyse treatment-naïve and treatment-experienced patients separately. In addition, we conduct economic analysis of genotype 4, non-cirrhotic, treatment-naïve and experienced patients. These patient groups reflect the licensed indications for the AbbVie Regimen, as well as patient populations studied in the SAPPHIRE I and II, the PEARL I, II, III and IV, and TURQUOISE II clinical trials.

Model structure

7.2.2 **Please provide a diagrammatical representation of the model you have chosen.**

The structure of the natural history model is similar to previously published models assessed in the UK, namely, Shepherd et al., 2007[57] and Hartwell et al., 2011[51] as is explained in detail in section 7.2.3. The model simulates the lifetime disease progression of persons with chronic HCV infection (Figure 23: Natural history model schematic). The same model structure is used for treatment-naïve and treatment-experienced patients with genotype 1 and genotype 4.

Figure 23: Natural history model schematic



Note: Health states are depicted by ellipses, while 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.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model structure is aligned with the clinical pathway of care described in section 2.5. The key outcome of interest in the clinical trials is SVR, defined as undetectable HCV RNA in the serum for at least 3 months after treatment cessation. As such, all treatment and treatment-related outcomes occur within the first model year, which coincides with the first cycle in the current model structure. Intervention with the AbbVie Regimen involves 12 or 24 weeks of therapy.

Natural History Model

AbbVie has based its HCV natural history model on previously published models of the natural history of chronic HCV infection (Shepherd et al., 2007; Hartwell et al., 2011). The model schematic shows six health states indicating progressive liver disease (i.e., mild chronic HCV, moderate chronic HCV, compensated cirrhosis, decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC) and liver transplant), three states representing recovered states, namely SVR (i.e., recovered, history of mild disease; recovered, history of moderate disease; recovered, history of compensated cirrhosis), and death (absorbing health state for liver death and non-liver death). DCC, HCC and liver transplant have health states for initial and subsequent years, not represented in the figure. AbbVie assumes that the natural history of genotype 1 and 4 are similar[62,63]

Consistent with Shepherd et al., 2007[57] and Hartwell et al., 2011[51] the three initial fibrosis stages are characterised by mild fibrosis (Metavir score F0-F1), moderate fibrosis (F2-F3), and compensated cirrhosis (F4), with possible transitions occurring annually. Patients with bridging fibrosis (F3) are included in the moderate health state rather than compensated cirrhosis (CC), which may bias against antiviral therapy; this is because the observed SVR rates in F3 patients tend to be lower than in F2 patients given their greater severity of liver disease thus bringing the average SVR across moderate fibrosis down.

Patients initiate treatment in the first model year. Patients who do not achieve SVR are at risk of progressive liver disease, and are assumed to face the same risks of disease progression as untreated patients. In the absence of successful treatment, patients may remain in their existing health state or may progress to more severe stages of liver disease. A proportion of patients with compensated cirrhosis progress to DCC and HCC[64,65] Although DCC can present simultaneously in multiple forms in any individual patient, based on the expert opinion, historical models and the constraints of a Markov model, we decided to model DCC as a single health state (e.g., Shepherd et al., 2007[57], Grishchenko et al., 2009;[66] Hartwell et al., 2011[51]).

A proportion of patients with DCC receive liver transplants. Patients with HCC may also receive liver transplants, which was not applied in the base case of Hartwell et al., 2011[51]but is aligned with feedback from external experts consulted in the UK and is a feature in recent models (e.g., Liu et al., 2012).[67, 68,69]

In the base case, we use transitional probabilities described in Shepherd et al., 2007[57] which were in turn sourced from the economic evaluation undertaken alongside the UK Mild hepatitis C Trial.[70] In sensitivity analysis, we also assess results using transitional probabilities from Grishchenko et al., 2009 who assumed different fibrosis progression rates by age at presentation for treatment (30 versus 40 versus 50 years old). Given the low probability of spontaneous clearance of chronic HCV, we opted not to include this in the base case. In addition, inclusion criteria across AbbVie's trials required patients to be positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before screening, and positive for HCV RNA and anti-HCV Ab at the time of screening minimising the chances of patients with spontaneous clearance to enrol into the trials.

The model uses a one-year cycle length (e.g., Shepherd et al., 2007; Grishchenko et al., 2009; Hartwell et al., 2011), which is aligned with epidemiologic data in the literature, and is also short relative to the model horizon (i.e., lifetime). Half-year cycle corrections are applied (Shepherd et al., 2007 and Hartwell et al., 2011). Costs and outcomes (QALYs) are discounted at 3.5% in the base case, which is aligned with the NICE methods guide. The model assumes 70-year timeframe, approximating the lifetime of treatment-naïve patient cohort with an average age of 40 at baseline and treatment-experienced cohort with an average age of 45. The baseline distribution of patients across stages of liver disease is based on Shepherd et al. 2007[57] that in turn uses the data reported from a clinical audit of patients attending a liver clinic at a London teaching hospital for treatment of their HCV.[71] In the base case, we further assume that 68.8% of genotype 1 patients have sub-genotype 1a.[72], have an average body weight of 66kg to 80kg and 70% are males.[57]

Effects of SVR and assumptions about Recovered states

With successful treatment, patients achieve SVR; the model assumes this to be a permanent condition unless re-infected; this means that patients with an SVR are assumed not to progress to more severe liver disease, other than those with history of CC (ellipses shaded in blue). There is robust clinical data to support that SVR suspends liver fibrosis progression. Pearlman et al., 2011 found in a review of literature that patients with SVR have significantly fewer liver-related complications, fewer HCCs, and fewer liver-related deaths; the authors also found that SVR is durable, with the incidence of late relapse extremely low (<1%). The authors conclude that SVR is a clinically meaningful endpoint and a durable marker of viral eradication.[73] In European analysis conducted by Veldt el al., 2004, the 5-year survival rate among patients achieving SVR was comparable to that of the general population, matched for age and sex.[74]

More recent literature such as Morisco et al., 2013,[75] Papastergiou et al., 2013,[76] and Koh et al., 2013[77], also suggest a favourable prognosis for patients with chronic HCV who achieved SVR. There is general acceptance that SVR is a reliable marker of positive long-term sequelae and, accordingly, we assume that attainment of SVR will reduce the probability of downstream HCV-associated morbidity and mortality. In the model, we therefore estimate the impact of an intermediate endpoint, namely SVR, on the long-term health outcomes, including QALYs, for patients with chronic HCV.

Re-infection

Patients who achieve SVR are assumed to face a small constant risk of reinfection if they continue to expose themselves to potential HCV infection or conduct risk taking behaviours associated with HCV infection. The likelihood of reinfection is based on a transitional probability of 1% per year, as per expert opinion. If re-infected, we assume that patients return to their initial fibrosis state.

HCC post-SVR limited to patients with cirrhosis; stratification for recovered states

The development of HCC after SVR is assumed for patients with cirrhosis, who after clearing the virus may still remain at increased risk of developing HCC compared to non-cirrhotic patients. This is consistent with the finding by Veldt et al., 2004.[78] Further, Poynard et al., 2002 pooled data from 3010 treatment-naïve patients from four randomised trials. They found that patients who achieve an SVR from mild or moderate chronic HCV have the same mortality risk and the risk of developing HCC, as the general population.[79] However, long-term risk of developing HCC remains for patients with cirrhosis up to 8 years in.[80] In a retrospective study published by Bruno et al., 2007 of 920 patients with cirrhosis treated with interferon, the incidence rate of HCC was 0.66 per 100 person-years among those who achieved SVR and 2.10 per 100 person-years among those who did not achieve SVR.[81] AbbVie aligns its model to all the above evidence. Thus, patients who have progressed to compensated cirrhosis are assumed to have an excess risk of HCC, even after achieving SVR, which they continue to be monitored for. We reference Cardoso et al., 2010 as the source of the transition probability from the "Recovered, history of compensated cirrhosis" health state to HCC.[82]

In summary, AbbVie's model stratifies patients who achieve SVR (i.e., those who cure the infection and transition to recovered health states) by fibrosis severity (i.e., mild, moderate, compensated cirrhosis), which is consistent with Hartwell et al., 2011. This is to account for differences in risk for patients entering the SVR state from different stages of chronic liver disease: patients who achieve SVR from mild or moderate chronic HCV are assumed to have the same mortality risk, including risk of developing HCC, as the general population, whereas those with history of compensated cirrhosis are assumed to have an excess risk of HCC even after viral infection has been eradicated. This is illustrated in the model schematic in Section 7.2.2.

Death from liver disease occurs from the DCC, HCC or liver transplant states; death from other causes can occur from any state. As per the above paragraph, following SVR, patients with history of mild or moderate fibrosis are assumed to have the same mortality risk as that of the general population. Patients with compensated cirrhosis too are assumed to have the same mortality as that of the general population; however they may still develop HCC after they clear the virus. Lastly, the states represented by more advanced liver disease, namely decompensated liver disease, HCC and those who undergo liver transplant, are commonly accepted as distinct

stages of progressive liver disease and as such, carry excess mortality risks (e.g., Salomon et al., 2003; Shepherd et al., 2007; Hartwell et al., 2011).[83,57,51]

7.2.4 Please define what the health states in the model are meant to capture.

The health states in the model capture the complete clinical pathway of HCV, as well as the effects of virologic cure - SVR. The initial health states in the model stratify HCV disease severity into mild, moderate and compensated cirrhosis based on metavir scores, which stages patients' risk for future sequelae. Patients with HCV presenting with these fibrosis stages are potential candidates for treatment. The initial cycle (i.e., year 1) of the model incorporates both the costs and disutilities associated with HCV treatment and its associated adverse events.

SVR is the key clinical outcome resulting from a successful treatment, which is captured by the Recovered states (post-SVR health states). In patients achieving SVR, the risk of progression to more severe health states is eliminated with exception of patients with history of cirrhosis. Patients with compensated cirrhosis maintain a residual risk of developing HCC despite clearing the HCV virus.

Patients who do not achieve SVR may remain in their original health state, or they may progress to more advanced stages of liver disease, including decompensated cirrhosis, HCC, and liver transplant. These health states are the most significant adverse consequences of liver disease arising from HCV.

Given that life expectancy differs for those with HCV who are untreated or fail to achieve an SVR and those who have an SVR, mortality is included in the model.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model structure reflects two main aspects of HCV: a treatment component which captures the efficacy of active treatments in terms of sustained viral response (SVR) allowing patients with HCV to clear the virus and a natural history component which simulates the lifetime disease progression of patients with HCV following unsuccessful treatment with anti-viral therapy.

The progression of liver disease as a result of chronic infection with HCV usually develops over 20-50 years. In the initial stages of the disease, patients may be asymptomatic or may present with mild and non-specific symptoms (e.g., fatigue, flu-like symptoms, depression, cognitive impairment), which in turn adversely affects health-related quality-of-life (HRQL). As liver disease progresses, some patients develop cirrhosis and eventually progress from a compensated to decompensated state, HCC and liver failure requiring liver transplant. Our model, as mentioned above, captures this natural course of disease progression in patients who are

treated unsuccessfully with antiviral therapy. For those patients who respond successfully to antiviral treatment, the post-SVR health state is conditioned on their severity of fibrosis at treatment initiation. Patients who achieve SVR are also assumed to face a small constant risk of reinfection if they continue to expose themselves to risk of HCV infection. In summary, our model structure, as illustrated in the model schematic in section 7.2.2, captures key aspects of chronic HCV infection including a prospect of a successful treatment and viral eradication as well as the progressive nature of the disease in patients who do not clear the virus following anti-viral therapy.

7.2.6 **Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.**

Table 70: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime	Life-time analysis allows for the natural history of chronic HCV to be fully captured, including its long term consequences such as cirrhosis, hepatocellular carcinoma (liver cancer), end stage liver disease (ESLD), and death. It will also allow for the differences in costs and health outcomes between the technologies being compared to be fully appreciated. Life-time analysis is consistent with the scope of previous NICE appraisals for HCV treatment regimens.	Hartwell et al. 2011; Grischenko et al. 2009; Shepherd et al. 2007.
Cycle length	Annual	Assumption on annual cycle length is consistent with previous models. Annual cycle reflects relatively slow disease progression.	Hartwell et al. 2011; Grischenko et al. 2009; Shepherd et al. 2007.
Half-cycle correction	Half-cycle correction included	Patients transition between health states throughout the cycle, and not only at the start and end of each cycle. Current model is consistent with previous models.	Hartwell et al. 2011; Shepherd et al. 2007.
Were health effects measured in QALYs; if not, what was used?	QALYs	Current model is consistent with previous models, and aligned with NICE methods guide	Hartwell et al. 2011; Grischenko et al. 2009; Shepherd et al. 2007; NICE methods 2013.
Discount of 3.5% for utilities and costs	3.5%	Current model is consistent with previous models, and aligned with NICE methods guide	Hartwell et al. 2011; Grischenko et al. 2009; Shepherd et al. 2007; NICE methods 2013.
Perspective (NHS/PSS)	NHS and PSS	Current model is consistent with previous models, and aligned with NICE methods guide	Hartwell et al. 2011; Grischenko et al. 2009; Shepherd et al. 2007; NICE methods 2013.

NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years

Technology

7.2.7 **Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?**

For genotype 1 treatment-naïve and treatment-experienced patients, the intervention, the AbbVie Regimen, and its comparators (sofosbuvir + PR, telaprevir + PR, boceprevir + PR and PR alone) are implemented in the model as per their marketing authorisations and licensed indications, and therefore are directly relevant to the comparisons listed in the decision problem.

For genotype 4 treatment-naïve and treatment-experienced patients, the AbbVie Regimen and the comparator (sofosbuvir + PR and PR alone), are implemented in the model as per their marketing authorisations and licensed indications and therefore are directly relevant to the comparison listed in the decision problem.

7.2.8 **Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators**.

The stopping rules incorporated into the economic model are consistent with those implemented in the clinical trials. We describe this in detail below.
First, there are no continuation rules for the AbbVie Regimen, sofosbuvir + PR for genotype 1 and 4 patients, and PR alone in genotype 4 treatment-naïve patients used in the economic model.

Stopping rules for other products are implemented based on their pivotal trials. Stopping rules for telaprevir are implemented in our model based on the ADVANCE[85] and REALIZE[91] trials to prevent the continuation of treatment in patients who did not have an adequate early response. The stopping rules in REALIZE are marginally more restrictive than in the ADVANCE trial. Modelling trial-based stopping rules impacts on the overall mean treatment duration for each respective therapy biasing the regimen cost in their favor. For example, the mean treatment duration for

telaprevir in the ADVANCE trial was 10.7 weeks versus the intended 12 weeks (as per SPC) which assumes there is no drug wastage. Stopping rules allowed for PR in genotype 1 treatment-naïve and -experienced patients were based on the TPR arms of the ADVANCE and REALIZE trials respectively. For further details, please refer to section 7.5.1 of the submission.

Stopping rules for boceprevir are implemented in our model based on the SPRINT-2[90] and RESPOND-2 trials[94]. In all 3 groups in SPRINT-2 study treatment was discontinued for all patients with a detectable HCV RNA level at week 24, according to standard futility rule. Boceprevir treatment could be discontinued, but peginterferon-ribavirin could be continued for up to 48 weeks with appropriate clinical follow up, per criteria described in those trials. In all groups in RESPOND-2, failure to achieve an undetectable HCV RNA level at week 12 resulted in discontinuation of all treatment and advancement to follow-up. In addition, a 12-week stopping rule was applied to patients in the response-guided therapy group (consisting of boceprevir plus peginterferon-ribarvirin for 32 weeks), per criteria described in those trials.

7.3 Clinical parameters and variables

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Consistent with the model structure described in Section 7.2, the treatment-specific clinical data implemented into the model are: SVR rates, AE rates, treatment duration, and treatment-related health utilities (see Table 71 below). In the model, we use observed clinical trials outcomes for the AbbVie Regimen and its comparators. We model five key AEs: anaemia, depression, rash, grade 3/4 neutropenia and grade 3/4 thrombocytopenia. Consistent with clinical trial reporting, we assume that AEs are treatment and duration specific, and independent of patient characteristics like fibrosis severity or genotype/sub-genotype. When data for a given AE is missing, we make a conservative assumption that the AE was not observed. In deterministic sensitivity analysis (DSA), we vary these treatment attributes; discussed in detail in Section 7.6.2.

Table 71: Clinical data and their sources implemented in the cost-effectiveness model

	Variable	Source
Patient characteristics	Age, weight and gender distribution at model entry Fibrosis distribution at baseline	Hartwell et al. 2011[51]; Shepherd et al. 2007[57] (see section 7.2.3)
	Distribution of prior non response to PR among treatment experienced patients (prior null/partial/relapse)	Expert Opinion
Treatment related variables	SVR rates	For AbbVie pivotal clinical trials see sections 7.3.1 further below; derivation of

	Treatment related AEs Treatment duration	treatment durations from trial publications is described in Section 7.5
Health Related Quality of Life (HRQoL)	Treatment-related quality of life (on treatment utility reduction)	Derivation of treatment-related health utilities from clinical trial data/publications is described in Section 7.4

Patient characteristics:

Baseline characteristics of the modelled cohorts were sourced from Hartwell et al. 2011[51] and Shepherd et al. 2007[57] studies reporting relevant characteristics for the UK population of patients with chronic hepatitis C. Modelling patient age enables relevant age-specific all-cause mortality rates to be applied to patients as they progress through the model.

The incorporation of disease severity upon entry into the model (mild/moderate/CC) allows for SVR rates specific to the stage of liver fibrosis to be applied to patients occupying these respective health states. Further, baseline characteristics of the treatment experienced cohort allow for the type of prior non-response to PR (null/partial/relapse) to be incorporated into the model.

Treatment characteristics:

Observed clinical outcomes from AbbVie pivotal trials and all the comparator trials are used in the model to calculate the probability of patients achieving SVR following treatment. Therefore SVR rates from the trials (intention-to-treat perspective) directly determine transition probabilities of patients moving from their baseline health state (mild/moderate/CC) into the recovered health state (retaining the memory about their stage of disease prior to SVR) following successful treatment; however in the absence of successful treatment, patients either remain in their respective health state or they progress to more severe stages of liver disease. SVRs are determined separately for treatment naïve and treatment experienced patients (null/partials/relapsers). Similarly, treatment related AEs for all therapies have been sourced from their respective clinical trials. Thus the rates of five key AEs: rash, depression, anaemia, grade 3/4 neutropenia and thrombocytopenia have been incorporated into the model so that the resource use associated with their management can be estimated.

Observed clinical trial outcome values (SVR and AEs):

In this section, we describe the observed clinical trials outcomes for the interventions that were applied in the model. In all cases we use an intention-to-treat (ITT) perspective.

<u>The AbbVie HCV regimens</u>:

Table 72 below summarises observed SVR rates directly applied in the model for AbbVie's 3D and 2D regimens:

Table 72: Reported SVR rates for trials containing AbbVie regimen

Treatment Status	GT/ SubGT	Fibrosis Stage	AbbVie Regimen	Trial	SVR Rate	n	N
Naïve	1a	No Cirrhosis	+R/12 weeks	SAPPHIRE I	**95.7%[Ω] (308/322)**	**308**	**322**
Naïve	1a	No Cirrhosis	+R/12 weeks	PEARL IV	**97.0%[^] (97/100)**	**97**	**100**
Naïve	1a	Cirrhosis	+R/12 weeks	TURQUOISE II	**92.2%[^] (59/64)**	**59**	**64**
Naïve	1a	Cirrhosis	+R/24 weeks	TURQUOISE II	**94.6%[Ω] (53/56)**	**53**	**56**
Naïve	1b	No Cirrhosis	-R/12 weeks	PEARL III	**100.0%[Ω] (209/209)**	**209**	**209**
Naïve	1b	Cirrhosis	+R/12 weeks	TURQUOISE II	**100.0%[+] (22/22)**	**22**	**22**
Null Response	1a	No Cirrhosis	+R/12 weeks	SAPPHIRE II	**95.4%** (83/87)**	**83**	**87**
Experienced	1a	Cirrhosis	+R/12 weeks	TURQUOISE II	**85.5%[^] (65/76)**	**65**	**76**
Experienced	1a	Cirrhosis	+R/24 weeks	TURQUOISE II	**95.4%[^] (62/65)**	**62**	**65**
Null Response	1a	Cirrhosis	+R/12 weeks	TURQUOISE II	**80.0%[^] (40/50)**	**40**	**50**
Null Response	1a	Cirrhosis	+R/24 weeks	TURQUOISE II	**92.9%[+] (39/42)**	**39**	**42**
Partial Response	1a	No Cirrhosis	+R/12 weeks	SAPPHIRE II	**100.0%** (36/36)**	**36**	**36**
Partial Response	1a	Cirrhosis	+R/12 weeks	TURQUOISE II	**100.0%[^] (11/11)**	**11**	**11**
Partial Response	1a	Cirrhosis	+R/24 weeks	TURQUOISE II	**100.0%[^] (10/10)**	**10**	**10**
Prior Relapse	1a	No Cirrhosis	+R/12 weeks	SAPPHIRE II	**94.0%** (47/50)**	**47**	**50**
Prior Relapse	1a	Cirrhosis	+R/12 weeks	TURQUOISE II	**93.3%[^] (14/15)**	**14**	**15**
Prior Relapse	1a	Cirrhosis	+R/24 weeks	TURQUOISE II	**100.0%[^] (13/13)**	**13**	**13**
Null Response	1b	No Cirrhosis	-R/12 weeks	PEARL II	**100.0%[#] (32/32)**	**32**	**32**
Null Response	1b	Cirrhosis	+R/12 weeks	TURQUOISE II	**100.0%[+] (25/25)**	**25**	**25**
Partial Response	1b	No Cirrhosis	-R/12 weeks	PEARL II	**100.0%[#] (26/26)**	**26**	**26**
Partial Response	1b	Cirrhosis	+R/12 weeks	TURQUOISE II	**85.7%[+] (6/7)**	**6**	**7**
Prior Relapse	1b	No Cirrhosis	-R/12 weeks	PEARL II	**100.0%[#] (33/33)**	**33**	**33**
Prior Relapse	1b	Cirrhosis	+R/12 weeks	TURQUOISE II	**100.0%[+] (14/14)**	**14**	**14**
Naïve	4	No Cirrhosis	+R/12 weeks	PEARL I	**100.0%[++] (42/42)**	**42**	**42**
Experienced	4	No Cirrhosis	+R/12 weeks	PEARL I	**100.0%[Ω] (49/49)**	**49**	**49**
Null Response	4	No Cirrhosis	+R/12 weeks	PEARL I	**100.0%[Ω] (23/23)**	**23**	**23**

Treatment Status	GT/ SubGT	Fibrosis Stage	AbbVie Regimen	Trial	SVR Rate	n	N
Partial Response	4	No Cirrhosis	+R/12 weeks	PEARL I	**100.0%** [Ω] **(9/9)**	**9**	**9**
Prior Relapse	4	No Cirrhosis	+R/12 weeks	PEARL I	**100.0%** [Ω] **(17/17)**	**17**	**17**

AbbVie Regimen = paritapevir/r–ombitasvir and dasabuvir ± R; Cirrhosis = compensated cirrhosis, F4; GT = genotype; No cirrhosis = mild/moderate fibrosis, F0-F3; R = ribavirin; SVR = sustained virologic response.
Data taken directly from clinical trial publication or CSR in **boldface** font.
Sources:
**Table S3 in Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370(17):1604-14.
[#]Table 2 in Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, Ritonavir, Ombitasvir, and Dasabuvir Achieves 97% and 100% Sustained Virologic Response With or Without Ribavirin in Treatment-Experienced Patients With HCV GT1b Infection. *Gastroenterology* 2014;147(2):359-65.
[+]Table 2 in Poordad F, Hezode C, Trinh R, et al. ABT-450/r–ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;370(21):1973-82.
[^]Per EMA label, GT1a patients with cirrhosis with favourable baseline laboratory indicators (i.e., AFP < 20 ng/mL, platelets ≥ 90 x 10^9/L, and albumin ≥ 35 g/L) have the same relapse rates irrespective of whether treated for 12 or 24 weeks and therefore a scenario has been presented where they may be considered for treatment with 3D+R for 12 weeks, while patients who do not meet this criteria are treated for 24 weeks. We test this in scenario analysis by weighting by the 12-week treatment arm's SVR in TURQUOISE II shown above
[++]Pol S, Reddy R, Baykal T et al. Interferon-free regimens of Ombitsasvir and ABT-450/r with or without ribavirin in patients with HCV genotype 4 infection: PEARL-I study results. Hepatology. AASLD Abstracts. 2014; 60(4):1129A.
[Ω]AbbVie SPC; Figure 2 in Feld et al. (2014) and Table 2 in Ferenci et al. (2014) published SVR = 307/322 and 207/209 respectively; however at the time of publications, one patient in Sapphire I and two in Pearl III did not have their SVR 12 data reported within defined visit window (before the primary database lock), and as such were classified as missing; however, during submission to EMA the agency requested that as per statistical analyses plans, for those three subjects SVR data were backwardly imputed, resulting in updated SVR rates. In Poordad et al. (2014) SVR for naïve GT1a F4 patient was 52/56 in the publication, but updated to 53/56 in the CSR when a missing patient's SVR became known. Updated PEARL I SVR data for treatment-experienced GT4 non-cirrhotic patients not yet published.
Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370(17):1594-603.

The clinical sections of this submission described phase III clinical trials of the AbbVie's HCV regimens, namely SAPPHIRE I and II, PEARL I, II, III and IV, and TURQUOISE II trials. Importantly, trials in genotype 1 patients reported SVR at post treatment week 12 (SVR12) separately for sub-genotype 1a and 1b. Moreover, trials for patients with cirrhosis were undertaken separately. As such, published data are found reporting SVRs stratified by sub-genotype and presence or absence of cirrhosis, but not further distinguishing between mild and moderate fibrosis. Thus, in our model base case we assume that patients with mild and moderate cirrhosis have the same SVR rates. However in one of our exploratory scenario analysis we use data from AbbVie CSRs which allowed stratification of SVR per mild and moderate fibrosis.

Further, both SAPPHIRE I (Arm A) and PEARL IV (Arm A) trials enrolled patients with sub-genotype 1a. The inclusion and exclusion criteria for both trials were almost identical; both trial arms recruited treatment-naïve, genotype 1a patients without cirrhosis to be treated with 3D + RBV. In our model, we thus pool the results for this subgroup of patients from these two trial arms by simply adding their numbers, to arrive at an overall SVR for genotype 1a naïve patients without cirrhosis (see Table 73 below).

Table 73: Overall combined SVR for AbbVie Regimen, GT1a naïve patients with no cirrhosis

Treatment Status	SubGT	Fibrosis Stage	Trial	SVR	n	N
Naïve	1a	No Cirrhosis	SAPPHIRE I and PEARL IV	96.0% (405/422)	405	422

Discontinuation rates for the AbbVie Regimen trials were very low ranging from 0% to under 2% for all 12 week regimens, and 5.2% for the 24 week arm of TURQUOISE II, which was in patients with cirrhosis. Adverse event results although reported by trial arm were not reported by sub-genotype. For instance, in SAPPHIRE I, adverse events were reported for all G1 patients in the 3D arm including ribavirin, regardless of their sub-genotype; in TURQUOISE II, adverse events were reported for all patients in each arm (Arm A= 12 weeks; Arm B=24 weeks), regardless of treatment experience and sub-genotype of patients within a given trial arm. Table 75 overleaf shows rates of adverse events for the AbbVie Regimen applied in the model. As we had done with the SVR above, in the model, we also combine the AEs between the SAPPHIRE I and PEARL IV treatment arms (Table 74 below).

Table 74: Overall AE for AbbVie regimen, GT1a naïve patients with no cirrhosis

Trial	Anaemia	Depression	Rash	Neutropenia	Thrombocytopenia	N
SAPPHIRE I and PEARL IV	31	0	56	0	0	573

Table 75: Selected adverse events in trials containing the AbbVie regimens

Treatment Status	GT/ SubGT	Fibrosis Stage	Trial	Anaemia (n)	Depression (n)	Rash (n)	Neutropenia (n)	Thrombo-cytopenia (n)	N
Naïve	GT1a	No cirrhosis	SAPPHIRE I	**25***	0	**51***	**0**[§]	**0**[§]	**473**
Naïve	GT1a	No cirrhosis	PEARL IV	**6**[+]	0	**5**[+]	**0**[§]	**0**[§]	**100**
Naïve	GT1a	Cirrhosis	TURQUOISE II	**16**[#]	**8**[#]	**23**[#]	**1**[§]	**2**[§]	**208**
Naïve	GT1b	No cirrhosis	PEARL III	**1**[++]	0	**8**[++]	**1**[§]	**1**[§]	**209**
Naïve	GT1b	Cirrhosis	TURQUOISE II	**16**[#]	**8**[#]	**23**[#]	**1**[§]	**2**[§]	**208**
Experienced	GT1a	No cirrhosis	SAPPHIRE II	**16**[^]	0	**26**[^]	**0**[§]	**0**[§]	**297**
Experienced (24 weeks)	GT1a	Cirrhosis	TURQUOISE II	**18**[#]	**12**[#]	**25**[#]	**3**[§]	**0**[§]	**172**
Experienced (12 weeks)	GT1a	Cirrhosis	TURQUOISE II	**16**[#]	**8**[#]	**23**[#]	**1**[§]	**2**[§]	**208**
Experienced	GT1b	No cirrhosis	PEARL II	**0**[Ω]	0	**1**[Ω]	**0**[§]	**0**[§]	**95**
Experienced	GT1b	Cirrhosis	TURQUOISE II	**16**[#]	**8**[#]	**23**[#]	**1**[§]	**2**[§]	**208**
Naïve	GT4	No cirrhosis	PEARL I	**1**[§]	**1**[§]	**2**[§]	**1**[§]	**0**[§]	**42**
Experienced	GT4	No cirrhosis	PEARL I[‡]	1	1	2	1	0	42

AbbVie Regimen = paritapevir/r–ombitasvir and dasabuvir ± R; AE = adverse event; Cirrhosis = compensated cirrhosis, F4; Experienced = null response, partial response, prior relapse; GT = genotype; No cirrhosis = mild/moderate fibrosis, F0-F3; R = ribavirin.
Data taken directly from clinical trial publication in **boldface** font. In the base case, we model GT1a cirrhotic patients receiving 24 week of treatment; AE data drawn from "Experienced (24 weeks)"
Only Grade 3-4 (<1x10^9/L) Neutropenia reported.
Only Grade 3-4 (<50 x 10^9/L) Thrombocytopenia reported.
For depression, a value of n=0 is assumed for trials where depression was not reported.
Sources:
*Calculated from Supplemental Table S5: Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370(17):1594-603.
[^]Supplementary Table 4 in Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370(17):1604-14.
[Ω]Table 3 in Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, Ritonavir, Ombitasvir, and Dasabuvir Achieves 97% and 100% Sustained Virologic Response With or Without Ribavirin in Treatment-Experienced Patients With HCV GT1b Infection. *Gastroenterology* 2014;147(2):359-65.
[+]Table S3 in Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r–ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014;370(21):1983-92.
[#]Table 4 in Poordad F, Hezode C, Trinh R, et al. ABT-450/r–ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;370(21):1973-82.
[++]Table S4 in Ferenci et al. (2014).
[#]Supplemental Table S7 in Poordad et al. (2014).
[§] AbbVie internal data from respective trials' CSR.
[‡]AEs in PEARL I, GT4 treatment-experienced patients are not available. We assume the same data as for PEARL I in treatment-naïve patients.

Observed clinical trials outcome values (SVRs and AEs) for the comparator regimens:

In this section, we describe the use of "unadjusted" efficacy data for the comparator regimens. By unadjusted, we mean results derived directly from trial publications whenever possible, and the use of extrapolated results for subgroups (e.g. sub-genotype 1a and compensated cirrhosis) when such efficacy results were not reported, using simple calculations and assumptions. We thus present unadjusted results for subgroups when reported, including individual fibrosis stages (mild, moderate and compensated cirrhosis) and sub-genotypes (1a and 1b). We extrapolate efficacy rates when results were unreported, usually for a sub-genotype and fibrosis stage combined. All results are summarised at the end of each section, with an indication of values that were reported (taken directly from a trial publication in **bold** font) and which were extrapolated based on the reported efficacy results.

The comparator regimens considered in our submission:

- *SOF + PR in GT1, treatment-naïve (IFN-eligible) patients: NEUTRINO trial*
- *TPR + PR in GT1, treatment-naïve (IFN-eligible) patients: ADVANCE trial*
- *PR in GT1, treatment-naïve (IFN-eligible) patients: ADVANCE trial*
- *BOC + PR in GT1, treatment-naïve (IFN-eligible) patients: SPRINT-2 trial*
- *TPR + PR in GT1, treatment-experienced (IFN-eligible) patients: REALIZE trial*
- *PR in GT1, treatment-experienced (IFN-eligible) patients: REALIZE trial*
- *BOC + PR in GT1, partial response and prior relapse (IFN-eligible) patients: RESPOND-2 trial*
- *SOF + PR in GT4, treatment-naïve (IFN-eligible) patients: NEUTRINO trial*
- *PR in GT4, treatment-naïve, non-cirrhotic (IFN-eligible) patients*
- *PR in GT4, treatment-experienced, non-cirrhotic (IFN-eligible) patients*
- *No Treatment (NT), GT1 and GT4, IFN-unsuitable patients*

Sofosbuvir + PR in Treatment Naïve, Genotype 1 patients: NEUTRINO trial

The SVR outcomes of sofosbuvir plus peginterferon-ribavirin (PR) as observed in the NEUTRINO trial were published by Lawitz et al., 2013.[84] The NEUTRINO trial was a single-group, open-label study, where a 12-week regimen of sofosbuvir + PR was administered to 327 treatment-naïve U.S. patients with HCV genotype 1, 4, 5, or 6. Sofosbuvir was administered orally at a dose of 400 mg once daily along with ribavirin, which was administered orally according to body weight (i.e.,1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight of ≥75 kg). Peginterferon alfa-2a was administered subcutaneously once weekly at a dose of 180 µg. In NEUTRINO, a majority of patients were infected with HCV genotype 1 (i.e., 69% genotype 1a and 20% genotype 1b). Moreover, 16.5% of patients (rounded to 17% for ease of communication) had compensated cirrhosis. Importantly, primary results were reported collectively for patients with HCV genotypes 1, 4, 5, or 6. Supplemental tables included outcomes for genotype 1a and genotype 1b patients, as well as for patients with cirrhosis compared to those without cirrhosis. Results were not reported separately for mild and moderate fibrosis (Metavir) stages; as such, results were assumed to be the same for both groups in our model. In the NICE Single Technology Appraisal of sofosbuvir[95] (currently

ongoing at the time of submission), SVR data from Lawitz et al. (2013) were updated, as one patient with GT1 who was <LLOQ at SVR4 and was "lost to follow-up=failure" at SVR12 was subsequently "found" and achieved SVR24. We include this patient in determining the SVR rates. The primary efficacy endpoint of NEUTRINO was SVR12, summarised in Table 76 below.

Table 76: Reported SVR for sofosbuvir + PR in treatment-naïve, genotype 1 patients: NEUTRINO trial

Treatment Status	Genotype/ Sub-genotype	Fibrosis Stages	Reported SVR	n	N
Treatment-naïve	GT1,4,5,6	Mild, moderate, compensated cirrhosis	**90.2% (295/327)**	**295**	**327**
Treatment-naïve	GT1,4,5,6	Mild, moderate	**92.3% (252/273)**	**252**	**273**
Treatment-naïve	GT1,4,5,6	Compensated cirrhosis	**79.6% (43/54)**	**43**	**54**
Treatment-naïve	GT1	Mild, moderate, compensated cirrhosis	**89.7% (262/292)**	**262**	**292**
Treatment-naïve	GT1	Mild, moderate	**91.7% (220/240)***	**220**	**240**
Treatment-naïve	GT1	Compensated cirrhosis	**80.8% (42/52)***	**42**	**52**
Treatment-naïve	GT1a	Mild, moderate, compensated cirrhosis	**91.6%(206/225)**	**206**	**225**
Treatment-naïve	GT1b	Mild, moderate, compensated cirrhosis	**81.8% (54/66)**	**54**	**66**

Data taken directly from Lawitz et al., 2013 (in bold font); Supplemental Table S3 in Lawitz et al. Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection. *N Engl J Med*. 2013;368:1878-1887.

* Updated data from SOF ACD. Single technology appraisal (STA) for Sofosbuvir - Chronic hepatitis C *National Institute for Health and Care Excellence* March 2014.

In order to populate the cost-effectiveness model with transition probabilities relevant to the model health states, we disaggregate the observed SVR rates for genotype 1 as well as sub-genotypes 1a and 1b by cirrhosis status (mild/moderate and compensated cirrhosis). The difference between SVR in patients with mild to moderate fibrosis (91.7%) and those with compensated cirrhosis (80.8%) across GT1 patients was 10.9% (91.7%-80.8%). We thus assume that on average, the SVR in cirrhosis patients is 10.9% lower than in non-cirrhosis patients. In addition, we assume that the proportion of cirrhotic patients with sub-genotypes 1a and 1b is the same as that observed in GT1 patients (18%). Using these two assumptions, we impute SVR of patients with cirrhosis and without cirrhosis for genotype 1 and sub-genotypes 1a and 1b in the following manner: assuming that the SVR of patients with compensated cirrhosis with genotype 1a is denoted by $SVR_{cc,1a}$, we express the overall SVR rate for genotype 1a as 91.6% = 0.18 * $SVR_{cc,1a}$ + (1-0.18) * ($SVR_{cc,1a}$ + 10.9%). Therefore, $SVR_{cc,1a}$ = 82.6%. Table 77 below shows results from our computations, where, for illustration, we verify that overall SVR for sub-genotype 1a, namely SVR_{1a} = (0.82 * 93.5%) + (0.18 * 82.6%) = 91.6%. Results may be similarly calculated for sub-genotype 1b.

Table 77: Reported and imputed SVR for sofosbuvir + PR in treatment-naïve, genotype 1a and 1b patients, by cirrhosis status: NEUTRINO trial

Treatment Status	GT/ Sub GT	Fibrosis Stage	Reported/ Imputed SVR	n	N
Naïve	GT1	Mild, moderate, compensated cirrhosis	**89.7%** (262/292)**	**262**	**292**
Naïve	GT1	Mild, moderate	**91.7%** (220/240)**	**220**	**240**
Naïve	GT1	Compensated cirrhosis	**80.8% (42/52)****	**42**	**52**
Naïve	GT1a	Mild, moderate, compensated cirrhosis	**91.6%* (206/225)**	**206**	**225**
Naïve	GT1a	Mild, moderate	93.5%[^]	172.90[#]	184.93[+]
Naïve	GT1a	Compensated cirrhosis	82.6%[^]	33.10[#]	40.07[+]
Naïve	GT1b	Mild, moderate, compensated cirrhosis	**81.8%* (54/66)**	**54**	**66**
Naïve	GT1b	Mild, moderate	83.8%[^]	45.44[#]	54.25[+]
Naïve	GT1b	Compensated cirrhosis	72.9%[^]	8.56[#]	11.75[+]

Data taken directly from clinical trial publication in **boldface** font.
[^]Imputed SVR rates; SVR is weighted by the proportion of cirrhosis (18%) and non-cirrhosis patients, and we assume the decrement in SVR rates from mild/moderate fibrosis to compensated cirrhosis (i.e., 10.9%) is the same for GT1 and GT1a and GT1b patients; see text.
[#]The imputed number of patients with SVR (n) is derived from the imputed SVR of that subgroup multiplied by and the total number of patients in that subgroup (N). Results are reported to 2 decimal places.
[+]The imputed total number of patients in a subgroup (N) is computed using the weighted average of patients by fibrosis status. We further assume that the distributions of fibrosis in sub-genotypes 1a and 1b are the same as in GT1, namely 82% mild and moderate, and 18% compensated cirrhosis. Results are reported to 2 decimal places.
Source:
*Supplemental Table S3 in Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013;368(20):1878-87.
**Single technology appraisal (STA) for Sofosbuvir - Chronic hepatitis C *National Institute for Health and Care Excellence* March 2014

Of the 327 patients enrolled in NEUTRINO, 7 (2.14%) discontinued treatment. Combined adverse event results were reported for genotype 1, 4, 5 or 6. Adverse events such as anaemia and rash were reported only for the entire cohort of 327 patients, with no distinction by genotype or cirrhosis status. Given the paucity of data, we assume adverse event rates across sub-genotypes are the same. In our model, we further assume that the rates of adverse events were similar between cirrhotic and non-cirrhotic chronic patients. Table 78 below shows rates of adverse events applied in the model.

Table 78: Selected adverse events for sofosbuvir + PR in treatment-naïve, genotype 1 patients: NEUTRINO trial

Event	Genotype	Fibrosis Stages	n (%)	N
Anaemia	GT1,4,5,6	Mild, moderate, compensated cirrhosis	**68**[^] (20.8)	327

Rash	GT1,4,5,6	Mild, moderate, compensated cirrhosis	**59**^ (18.0)	327
Depression	GT1,4,5,6	Mild, moderate, compensated cirrhosis	**31**# (9.48)	327
Neutropenia	GT1,4,5,6	Mild, moderate, compensated cirrhosis	**66**^ (20.2)	327
Thrombocytopenia	GT1,4,5,6	Mild, moderate, compensated cirrhosis	**1**^ (0.306)	327

^Adverse event values taken directly from Lawitz et al., 2013 in bold font. # Supplemental Table S9 in Lawitz et al., 2013.
Grade 3-4 (<1x10^9/L) Neutropenia reported.
Grade 3-4 (<50 x 10^9/L) Thrombocytopenia reported.

Telaprevir + PR in Treatment Naïve, Genotype 1 patients: ADVANCE trial[85]

ADVANCE was a randomised, double-blind, placebo-controlled phase 3 trial. Patients with HCV genotype 1 who were previously not treated for HCV infection were assigned into 3 treatment arms: T8PR, T12PR and PR. Telaprevir (T) was administered orally in two groups, T8PR and T12PR, at a dose of 750 mg every 8 hours for 8 and 12 weeks, respectively. In all three treatment arms, peginterferon alfa-2a (P) was administered subcutaneously once weekly at a dose of 180 µg, while ribavirin (R) was administered orally at a dose according to body weight (i.e., 1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight of ≥75 kg). The treatment duration of peginterferon-ribavirin (PR) varied, as is described in detail below.

ADVANCE compared the SVR at post-treatment week 24 (SVR24) of patients in the telaprevir arms with those in the PR-only group. SVR as recorded in the T12PR treatment arm only is used directly in the model as it corresponds with the licensed indication for telaprevir. In the T12PR group, the total duration of treatment was either 24 or 48 weeks. During the first 12 weeks, 363 patients in the T12PR group received telaprevir + PR. A treatment rule was employed based on extended rapid virologic response (defined as undetectable HCV RNA at weeks 4 and 12); patients in the T12PR group who met the response criteria received 12 additional weeks of treatment with PR alone, leading to total treatment duration of 24 weeks. Patients in the T12PR group who did not meet the criteria received 36 additional weeks of treatment with PR, leading to total treatment duration of 48 weeks. Stopping rules were implemented to prevent the continuation of treatment in patients who did not achieve adequate response, including:

1. patients receiving telaprevir who had HCV RNA levels greater than 1000 IU per millilitre at week 4 discontinued telaprevir but continued PR;
2. all patients with less than a 2 log10 decrease from baseline in HCV RNA levels at week 12 discontinued treatment; and
3. patients discontinued treatment if HCV RNA was confirmed to be detectable at any time between weeks 24 and 40.

In our model we use outcome figures directly from Jacobson et al., 2011.[85] Sub-genotypes 1a and 1b accounted for 59% and 41% of the patients in T12PR, respectively[85]. The Table 79 below shows SVR rates across sub-genotypes 1a and 1b.

Table 79: Reported SVR for telaprevir + PR in treatment-naïve, genotype 1 patients: ADVANCE trial, T12PR arm

Treatment Status	Genotype/ Sub-genotype	Fibrosis Stages	Reported SVR	n	N
Treatment-naïve	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**74.7%*** (**271/363**)	**271**	**363**
Treatment-naïve	GT1a	No/minimal, portal, bridging fibrosis, cirrhosis	**71.4%**^ (**152/213**)	**152**	**213**
Treatment-naïve	GT1b	No/minimal, portal, bridging fibrosis, cirrhosis	**79.2%**^ (**118/149**)	**118**	**149**

Data taken directly from Jacobson et al., 2011 in bold font;
*Table 2 and ^Figure 2 in Jacobson et al., 2011.[85]

Moreover, patient distribution in the T12PR arm across stages of fibrosis was as follows: 37% had no or minimal fibrosis, 43% portal fibrosis, 14% bridging fibrosis, and the remaining 6% had cirrhosis. ADVANCE also reported SVR by fibrosis. In our model, we consolidate these into 3 categories, namely mild (patients with no/mild minimal fibrosis), moderate (patients with portal and bridging fibrosis) or compensated cirrhosis. Table 80 below outlines the results.

Table 80: Reported SVR for telaprevir + PR in treatment-naïve, genotype 1 patients, by fibrosis stages: ADVANCE trial, T12PR arm

Treatment Status	Genotype	Fibrosis Stages (ADVANCE)	Fibrosis Stages (model)	Reported SVR	n	N
Treatment-naïve	GT1	No/minimal fibrosis	Mild	**81.3%** (**109/134**)	**109**	**134**
Treatment-naïve	GT1	Portal, bridging fibrosis	Moderate	**71.6%*** (**149/208**)	**149**	**208**
Treatment-naïve	GT1	Cirrhosis	Compensated cirrhosis	**61.9%** (**13/21**)	**13**	**21**

Data taken directly from Jacobson et al., 2011 in bold font;
*Figure 2 in Jacobson et al. 2011[85]

It can be noted that as fibrosis progresses from mild to moderate, SVR falls by 9.7%. SVR decreases by another 9.7% for those with compensated cirrhosis. We impute the SVR values for mild/moderate/CC health states of sub-genotypes 1a and 1b by assuming the same decrements in SVR rates between mild/moderate and CC observed in the overall GT1 patient population. For instance, assuming that the SVR of a patient with sub-genotype 1a with compensated cirrhosis is $SVR_{cc,1a}$, it can be calculated: 71.4% = 0.37 * ($SVR_{cc,1a}$ + 9.7% + 9.7%) + (0.43 + 0.14) * ($SVR_{cc,1a}$ + 9.7%) + 0.06 * $SVR_{cc,1a}$. As such, $SVR_{cc,1a}$ = 58.6%. Our results for sub-genotypes 1a and 1b are presented in Table 81 below. In our computations, we do not round off the proportion patients in each fibrosis category. This explains the difference between the values reported in the table and those which would have been obtained if 37%, 57% and 6% were applied.

Table 81: Reported and imputed SVR for telaprevir + PR in treatment-naïve patients, for sub-genotype 1a and 1b, by fibrosis stages: ADVANCE trial, T12PR arm

Treatment Status	Genotype/ Sub-genotype	Fibrosis Stages (ADVANCE)	Fibrosis Stages (model)	Reported/Imputed SVR	n	N
Treatment-naïve	GT1a	No/minimal, portal, bridging fibrosis, cirrhosis	Mild, moderate, compensated cirrhosis	**71.4%*** (**152/213**)	**152**	**213**
Treatment-naïve	GT1a	No/minimal fibrosis	Mild	78.0%[^]	61.37[#]	78.63[+]
Treatment-naïve	GT1a	Portal, bridging fibrosis	Moderate	68.3%[^]	83.41[#]	122.05[+]
Treatment-naïve	GT1a	Cirrhosis	Compensated cirrhosis	58.6%[^]	7.22[#]	12.32[+]
Treatment-naïve	GT1b	No/minimal, portal, bridging fibrosis, cirrhosis	Mild, moderate, compensated cirrhosis	**79.2%*** (**118/149**)	**118**	**149**
Treatment-naïve	GT1b	No/minimal fibrosis	Mild	85.9%[^]	47.24[#]	55.00[+]
Treatment-naïve	GT1b	Portal, bridging fibrosis	Moderate	76.2%[^]	65.04[#]	85.38[+]
Treatment-naïve	GT1b	Cirrhosis	Compensated cirrhosis	66.%[^]	5.73[#]	8.62[+]

Data taken directly from Jacobson et al., 2011 are in bold font;
[^]Overall SVR is weighted by the proportion of mild (37%), moderate (57%) and compensated cirrhosis (6%) patients; we assume the decrement in SVR rates from mild to moderate fibrosis (9.7%) and from moderate to compensated cirrhosis (9.7%) are the same for genotype 1 and sub-genotypes 1a and 1b patients; see text
[+]The imputed total number of patients in a subgroup (N) is calculated using the proportion of patients in each fibrosis stage * the overall N. Results are reported to 2 decimal places.
[#]The imputed number of patients with SVR (n) is derived from the imputed SVR of that subgroup multiplied by and the total number of patients in that subgroup (N). Results are reported to 2 decimal places.

Of the 363 patients enrolled in T12PR, 268 completed treatment[85]. Of those who discontinued treatment, 36 patients (9.9% of enrolled patients) discontinued treatment due to an adverse event (Figure 1 or Supplementary Table 2 in Jacobson et al., 2011). Consolidated adverse event results were reported for all patients, and our model assumes that adverse event profiles are the same across all fibrosis stages, and sub-genotypes. The Table 82 below summarises the adverse event findings for the T12PR group, which were uniformly applied in our model to all subgroups of patients.

Table 82: Selected adverse events for telaprevir + PR in treatment-naïve, genotype 1 patients: ADVANCE trial, T12PR arm

Event	Genotype	Fibrosis Stages	n (%)	N
Anaemia	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**135**[^] (37.2)	363

Rash	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**133**^ (36.6)	363
Depression	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**66**^ (18.2)	363
Neutropenia	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**37.14**^^ (10.2)	363
Thrombocytopenia	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**7.82**^^ (2.15)	363

Adverse events reported directly in Jacobson et al., 2011 and Kauffman et al., 2011 in bold font.
Combined Grade 3-4 Neutropenia and Grade 3-4 Thrombocytopenia reported in Kauffman et al., 2011 for ADVANCE and ILLUMINATE studies. We impute the weighted number of AE based on sample sizes, rounded to 2 decimal places:
N_Neutropenia= (72+11)*[342/(342+479)} + (8+2)*[21/(21+61)] = 37.14
N_Thrombocytopenia= (12+0)*[342/(342+479)} + (10+1)*[21/(21+61)] = 37.14
Sources:
^Supplementary Table 1 in Jacobson et al.[85]
^^Table 5 in Kauffman et al. 2011[86]

PR alone in Treatment Naïve, Genotype 1 patients: ADVANCE trial

There are numerous trials of peginterferon-ribavirin (PR) documenting SVRs in GT1 patients, published over a number of years. Originally, our intention was to model efficacy inputs using estimates from a mixed treatment comparison (MTC) for all products. However as a MTC was not feasible in this disease area, PR SVR estimates for Treatment naïve patients in our model base case are based on the SVRs of patients receiving peginterferon alfa-2a and ribavirin alone (PR group) in the ADVANCE trial. We realise that this may be deemed a limitation of our submission, however PR SVR estimates in the ADVANCE study are higher than those observed in the SPRINT-2 trial (a corresponding trial of boceprevir and peginterferon alfa-2b where observed SVR in GT1 Group 1 patients = 38%) making our assumption a conservative one. In addition, we explore this in scenario analyses where we apply SVR rates reported in McHutchinson et al., 2009[87] and Hadziyannis et al., 2004[88] studies. A total of 361 patients infected with HCV genotype 1 were included in the PR group of the ADVANCE trial. Patients in the PR group received placebo plus PR for 12 weeks, followed by PR alone for 36 additional weeks. As such, the treatment duration in the PR group was 48 weeks in total. Peginterferon alfa-2a was administered subcutaneously once weekly at a dose of 180 µg, while ribavirin was administered orally as a divided dose according to body weight (i.e., 1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight of ≥75 kg). Stopping rules were implemented to prevent the continuation of treatment in patients who did not achieve adequate response:

1. patients with less than a 2 $\log_{10}$ decrease from baseline in HCV RNA levels at week 12 discontinued treatment; and
2. patients discontinued treatment if HCV RNA was confirmed to be detectable at any time between weeks 24 and 40.

The distribution of sub-genotype 1a and 1b was very similar to the T12PR group, comprising 58% and 42% of patients in the PR group, respectively. We assume patients used PR as specified in the trial and take outcomes directly from Jacobson et al., 2011.[85] Table 83 below shows SVR across sub-genotypes 1a and 1b in the PR group.

Table 83: Reported SVR for PR in treatment-naïve, genotype 1 patients: ADVANCE trial, PR arm

Treatment Status	Genotype/ Sub-genotype	Fibrosis Stages	Reported SVR	n	N
Treatment-naïve	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**43.8%*** (**158/361**)	**158**	**361**
Treatment-naïve	GT1a	No/minimal, portal, bridging fibrosis, cirrhosis	**40.9%**^ (**85/208**)	**85**	**208**
Treatment-naïve	GT1b	No/minimal, portal, bridging fibrosis, cirrhosis	**48.3%**^ (**73/151**)	**73**	**151**

Data taken directly from Jacobson et al., 2011 in bold font;
Sources:
*Table 2 in Jacobson et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. *N Engl J Med.* 2011;364:2405-2416.
^Figure 2 in Jacobson et al., 2011.

In the PR group of ADVANCE, patient distribution across stages of fibrosis was as follows: 41% had no or minimal fibrosis, 39% portal fibrosis, 14% bridging fibrosis, and the remaining 6% had cirrhosis (Table 1 in Jacobson et al., 2011). The proportion of patients with cirrhosis in both the T12PR and PR groups were the same. In our model, we consolidate these into 3 categories, namely mild, moderate or compensated cirrhosis and present them in the

Table 84 below.

Table 84: Reported SVR for PR in treatment-naïve, genotype 1 patients, by fibrosis stages: ADVANCE trial, PR arm

Treatment Status	Genotype	Fibrosis Stages (ADVANCE)	Fibrosis Stages (model)	Reported SVR	n	N
Treatment-naïve	GT1	No/minimal fibrosis	Mild	**45.6%** (**67/147**)	**67**	**147**
Treatment-naïve	GT1	Portal, bridging fibrosis	Moderate	43.5%* (84/193)	84	193
Treatment-naïve	GT1	Cirrhosis	Compensated cirrhosis	**33.3%** (**7/21**)	**7**	**21**

Data taken directly from Jacobson et al., 2011 in bold font
*We computed SVR by dividing the number of patients achieving SVR with portal and bridging fibrosis (67 + 17 = 84) by the total number of patients with portal and bridging fibrosis (141 + 52 = 193).
Source: Figure 2 in Jacobson et al. *N Engl J Med.* 2011;364:2405-2416.

We observe that as fibrosis progresses from mild to moderate, SVR falls by 2.1%. As moderate fibrosis progresses to compensated cirrhosis, SVR decreases by a further 10.2%. We thus impute the SVR values for sub-genotypes 1a and 1b by assuming that these decrements in SVR rates are similar for both sub-genotypes. For instance, assuming the SVR of a patient with sub-genotype 1a and compensated cirrhosis is labelled as $SVR_{cc,1a}$ and taking that the overall SVR represents a weighted average of SVRs for mild, moderate and CC health states, it can be

calculated: 40.9% = 0.41 * ($SVR_{cc,1a}$ + 2.1% + 10.2%) + (0.39 + 0.14) * ($SVR_{cc,1a}$ + 10.2%) + 0.06 * $SVR_{cc,1a}$. Thus, $SVR_{cc,1a}$ = 30.4%. The Table 85 below tabulates the results for sub-genotypes 1a and 1b. In our calculations the proportion patients in each fibrosis category is not rounded off. This explains the difference between the values reported in the table and those which would have been obtained if rounded proportions of 41%, 53% and 6% respectively were applied in the calculations.

Table 85: Reported and imputed SVR for PR in treatment-naïve, sub-genotype 1a and 1b patients, by fibrosis stages: ADVANCE trial, PR arm

Treatment Status	Genotype/ Sub-genotype	Fibrosis Stages (ADVANCE)	Fibrosis Stages (model)	Reported / Imputed SVR	n	N
Treatment-naïve	GT1a	No/minimal, portal, bridging fibrosis, cirrhosis	Mild, moderate, compensated cirrhosis	**40.9%*** (**85/208**)	**85**	**208**
Treatment-naïve	GT1a	No/minimal fibrosis	Mild	42.7%^	36.15#	84.70+
Treatment-naïve	GT1a	Portal, bridging fibrosis	Moderate	40.6%^	45.17#	111.20+
Treatment-naïve	GT1a	Cirrhosis	Compensated cirrhosis	30.4%^	3.68#	12.10+
Treatment-naïve	GT1b	No/minimal, portal, bridging fibrosis, cirrhosis	Mild, moderate, compensated cirrhosis	**48.3%*** (**73/151**)	**73**	**151**
Treatment-naïve	GT1b	No/minimal fibrosis	Mild	50.2%^	30.84#	61.49+
Treatment-naïve	GT1b	Portal, bridging fibrosis	Moderate	48.1%^	38.83#	80.73+
Treatment-naïve	GT1b	Cirrhosis	Compensated cirrhosis	37.9%^	3.33#	8.78+

Data directly from Jacobson et al., 2011 are in bold font;
^Imputed SVR; see text.
+The imputed total number of patients in a subgroup (N) is calculated by multiplying the same distribution of fibrosis observed in genotype 1, namely 41% mild, 53% moderate, 6% compensated cirrhosis to the overll SVRs for sub-genotypes 1a and 1b. Results are reported to 2 decimal places.
#The imputed number of patients with SVR (n) is derived from the imputed SVR of that subgroup multiplied by and the total number of patients in that subgroup (N). Results are reported to 2 decimal places.
Source:
*Figure 2 in Jacobson et al.[85]

Of the 361 patients enrolled in the PR arm, 202 completed treatment (Figure 1 in Jacobson et al., 2011).[85] There were 26 patients (7.2% of enrolled) who discontinued treatment due to an adverse event (Figure 1 or Supplementary Table 2 in Jacobson et al., 2011). Consolidated adverse event results were reported for all patients, and we thus assume in our model that adverse event profiles are the same across all baseline fibrosis states and sub-genotypes. Table 86 below summarises the adverse

event findings for PR that were uniformly applied in our model to all subgroups of patients.

Table 86: Selected adverse events for PR in treatment-naïve, genotype 1 patients: ADVANCE trial, PR arm

Event	Genotype	Fibrosis Stages	n (%)	N
Anaemia	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**70**[^] (19.4)	361
Rash	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**88**[^] (24.4)	361
Depression	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**79**[^] (21.9)	361
Neutropenia	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**53**[^] (11.9)	361
Thrombocytopenia	GT1	No/minimal, portal, bridging fibrosis, cirrhosis	**2**[^^] (0.554)	361

Adverse events reported directly in Jacobson et al., 2011 and Kauffman et al., 2011 in bold font.
Grade 3-4 Neutropenia and Thrombocytopenia reported in Kauffman et al., 2011.
Sources:
[^]Supplementary Table 1 Jacobson et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. *N Engl J Med.* 2011;364:2405-2416.
[^^]Table 5 in Kauffman et al. [78]

In sensitivity analysis, we explore an alternative source of SVR data, namely Hadziyannis et al., 2004[88], for treatment with PR in treatment-naïve genotype 1 patients. We also assess McHutchinson et al., 2009[87] in a separate sensitivity analysis.

Lastly, previous HTAs and guidelines on treatment for HCV genotype 1 have shown peginterferon alpha-2a to be clinically equivalent to peginterferon alpha-2b.[89] Therefore, our model makes the same assumption, and uses both interchangeably.

Boceprevir + PR in Treatment-Naïve, Genotype 1 patients: SPRINT-2 trial

SPRINT-2 was a phase 3, double blind, placebo-controlled study in treatment-naïve genotype 1 patients. All patients received a 4-week lead-in phase with peginterferon-ribavirin (PR). Subsequent treatment was determined by the outcome of randomisation to one of three treatment arms. Group 1 (control arm) received an additional 44 weeks of PR plus placebo for a total treatment duration of 48 weeks. In Group 2, the response-guided treatment arm (RGT, N=368), patients with undetectable HCV RNA at weeks 8 and 24 received additional 24 weeks of boceprevir (BOC) + PR for a total treatment duration of 28 weeks, whereas patients with detectable HCV RNA between weeks 8 and 24 but undetectable at week 24 stopped BOC + PR at week 28, but then continued PR alone for a subsequent 20 weeks for a total treatment duration of 48 weeks. In the fixed duration treatment (FDT) group (Group 3), following 4 weeks lead in, 366 patients were administered BOC + PR for 44 weeks for a total treatmemt duration of 48 weeks. Patients received peginterferon alfa-2b subcutaneously at a dose of 1.5 µg per kilogram once weekly and weight-based ribavirin orally at a total dose between 600 to 1400 mg per

day. Boceprevir was taken orally at a dose of 800 mg every 7 to 9 hours. Primary efficacy endpoint was SVR24. The results were published in Poordad et al., 2011.[90] Although SVR was numerically higher in the FDT group than RGT group, the authors concluded that they were similar between both groups. Moreover, the cost of the FDT regimen would be significantly higher than the cost of the RGT regimen. In our model, we apply results from the overall more favourable RGT group.

Of the patients in the RGT group with genotype 1, 234 patients had sub-genotype 1a, and a vast majority (95%) had no cirrhosis. In the appendix of the publication, SVR rates were presented by cirrhosis status (i.e., cirrhosis vs. no cirrhosis) and by sub-genotype status. Table 87 below consolidates our findings.

Table 87: Reported SVR for boceprevir + PR in treatment-naïve, genotype 1 patients: SPRINT-2 trial

Treatment Status	Treatment Arm	Genotype/ Sub-genotype	Fibrosis Stages (SPRINT-2)	Reported SVR	n	N
Treatment-naïve	RGT	GT1	F0-F4	**63.3%*** (**233/368**)	**233**	**368**
Treatment-naïve	RGT	GT1	F0-F3	**65.9%**^ (**222/337**)	**222**	**337**
Treatment-naïve	RGT	GT1	F4	**31.3%**^ (**5/16**)	**5**	**16**
Treatment-naïve	RGT	GT1a	F0-F4	**59.2%**^ (**106/179**)	**106**	**179**
Treatment-naïve	RGT	GT1b	F0-F4	**66.4%**^ (**89/134**)	**89**	**134**

Data taken directly from Poordad et al., 2011 are in bold font;
There were patients with unknown sub-genotypes, therefore the overall number of patients with GT1 = 368, while the total number of patients with known G1a+G1b = 179+134=331.
Sources:
*Table 2 in Poordad et al. 2011;364:1195-1206.[90]
^Supplemental Figure S2A in Poordad et al., 2011.[90]

Since SVR data were reported in Sprint-2 for patients without and with cirrhosis, in the model we assume the same SVR for those with mild and moderate fibrosis. We impute SVR for sub-genotypes 1a and 1b, using the same methodology described previously. We observe that as fibrosis progresses from no cirrhosis to cirrhosis in the overall GT1, SVR falls by 34.6%. We further assume that this decrement in SVR rates holds true for both sub-genotypes. For instance, taking that the overall SVR represents a weighted average of SVRs for mild, moderate and CC health states and labelling the SVR of a patient with sub-genotype 1a and compensated cirrhosis as $SVR_{cc,1a,}$ it can be calculated: 59.2% = 0.95 * ($SVR_{cc,1a}$ + 34.6%) + 0.05 * $SVR_{cc,1a}$. Thus, $SVR_{cc,1a}$ = 26.2%. Table 88 below shows the imputed results.

Table 88: Reported and imputed SVR for boceprevir + PR in treatment-naïve, sub-genotype 1a and 1b patients, by fibrosis stages: SPRINT-2 trial

Treatment Status	Genotype/ Sub-genotype	Fibrosis Stages (SPRI	Fibrosis Stages (model)	Reported / Imputed SVR	n	N

		NT-2)				
Treatment-naïve	GT1a	F0-F4	Mild, moderate, compensated cirrhosis	**59.2%*** (**106/179**)	**106**	**179**
Treatment-naïve	GT1a	F0-F3	Mild, moderate cirrhosis	60.8%^	103.88#	170.89+
Treatment-naïve	GT1a	F4	Compensated cirrhosis	26.2%^	2.12#	8.11+
Treatment-naïve	GT1b	F0-F4	Mild, moderate, compensated cirrhosis	**66.4%*** (**89/134**)	**89**	**134**
Treatment-naïve	GT1b	F0-F3	Mild, moderate cirrhosis	68.0^	86.97#	127.93+
Treatment-naïve	GT1b	F4	Compensated cirrhosis	33.4%^	2.03#	6.07+

Data directly from Poordad et al., 2011 are in bold font;
^SVR imputed; see text.
#The imputed number of patients with SVR (n) is derived from the imputed SVR of that subgroup multiplied by the total number of patients in that subgroup (N). Results are reported to 2 decimal places.
+The imputed total number of patients in a subgroup (N); Results are reported to 2 decimal places.
Source:
*Supplemental Figure S2A in Poordad et al., 2011[90]

Of the 368 patients enrolled in the RGT arm, 45 (12.2%) discontinued treatment due to an adverse event (Table S2A in Poordad et al., 2011). Consolidated adverse event results were reported for all patients, and we assume in our model that adverse event profiles are the same across fibrosis states. Table 89 below summarises the adverse event findings for the RGT arm that were uniformly applied in our model to all subgroups of patients.

Table 89: Selected adverse events for boceprevir + PR in treatment-naïve, genotype 1 patients: SPRINT-2 trial

Event	Genotype	Fibrosis Stages	n (%)	N
Anaemia	GT1	F0-F4	**182**^ (49.5)	368
Rash	GT1	F0-F4	**93**^ (25.3)	368
Depression	GT1	F0-F4	**83**^ (22.6)	368
Neutropenia	GT1	F0-F4	**108*** (29.3)	368
Thrombocytopenia	GT1	F0-F4	**12*** (3.3)	368

Adverse events in bold font are reported in Poordad et al., 2011.
Only Grade 3-4 (<1x10^9/L) Neutropenia reported.
Only Grade 3-4 (<50 x 10^9/L) Thrombocytopenia reported.
Sources:
*Table 3 Poordad et al. 2011;364:1195-1206[90]

^Supplementary Table S2B in Poordad et al., 2011;364:1195-1206[90]

Sofosbuvir (SOF) + PR in Treatment Experienced, Genotype 1 patients

No trials were conducted with sofosbuvir + PR in treatment-experienced, genotype 1 patients. Our comparators for treatment-experienced patients will be telaprevir + PR, boceprevir + PR and PR alone (details below).

Telaprevir + PR in Treatment-Experienced, Genotype 1 patients: REALIZE trial

We employ in the model the observed SVR24 of treatment-experienced HCV genotype 1 patients treated with telaprevir + PR. Specifically, treatment-experienced patients were categorised into: prior null response, prior partial response or prior relapse.[91] REALIZE was a randomised, phase 3 trial with three treatment arms. We do not include the lead-in group of the REALIZE trial in our analysis as the telaprevir licensed indication not support a 4-week lead-in with PR. In the T12PR48 group, 266 treatment-experienced patients received telaprevir + PR for 12 weeks, followed by PR for another 36 weeks (total treatment duration of 48 weeks). Dosing was similar to the ADVANCE T12PR group. The difference in treatment regimen between the T12PR48 group (REALIZE) and the T12PR group (ADVANCE) was the following: T12PR patients were given either a total of 24 or 48 weeks of PR depending on viral response, whereas T12PR48 patients were always given a total of 48 weeks of PR. Stopping rules were applied to all patients in T12PR48, the details of which may be found in Zeuzem et al., 2011.[91]

Zeuzem et al. (2011) reported the combined SVR of F3-F4 patients; however in the CHMP Assessment report (Table 42-44 in CHMP AR: Incivo (telaprevir) Procedure No.: EMEA/H/C/002313 *European Medicines Agency* July 2011)[92] data for GT1 patients were stratified by fibrosis severity (mild, moderate, compensated disease). We impute the SVR rates for sub-genotypes 1a and 1b using the same assumptions and methodology as previously described. Our results are tabulated below.

Table 90: Reported and imputed SVR for telaprevir + PR by treatment experience and fibrosis stages: REALIZE trial, T12PR48 arm

Treatment Status	GT/ SubGT	Fibrosis Stage (REALIZE)	Fibrosis Stage (model)	Reported/ Imputed SVR	n	N
Null response	GT1	F0-F4	Mild, moderate, compensated cirrhosis	**29.2%*** (**21/72**)	**21**	**72**
Null response	GT1	F0-F1	Mild	**10.0%*** **(1/10)**	**1**	**10**
Null response	GT1	F2-F3	Moderate	**47.1%*** **(15/36)**	**15**	**36**
Null response	GT1	F4	Compensated cirrhosis	**19.2%*** **(5/26)**	**5**	**26**
Null response	GT1a	F0-F4	Mild, moderate, compensated cirrhosis	**24.4%*** **(11/45)**	**11**	**45**
Null response	GT1a	F0-F1	Mild	5.3%^	0.33#	6.25+
Null response	GT1a	F2-F3	Moderate	36.9%^	8.31#	22.50+

Null response	GT1a	F4	Compensated cirrhosis	14.5%^	2.36#	16.25+
Null response	GT1b	F0-F4	Mild, moderate, compensated cirrhosis	**37.0%* (10/27)**	**10**	**27**
Null response	GT1b	F0-F1	Mild	17.9%^	0.67#	3.75+
Null response	GT1b	F2-F3	Moderate	49.5%^	6.69#	13.50+
Null response	GT1b	F3-F4	Compensated cirrhosis	27.1%^	2.64#	9.75+
Partial response	GT1	F0-F4	Mild, moderate, compensated cirrhosis	**59.2%* (29/49)**	**29**	**49**
Partial response	GT1	F0-F1	Mild	**71.4%* (5/7)**	**5**	**7**
Partial response	GT1	F2-F3	Moderate	**75.0%* (18/24)**	**18**	**24**
Partial response	GT1	F4	Compensated cirrhosis	**33.3%* (6/18)**	**6**	**18**
Partial response	GT1a	F0-F4	Mild, moderate, compensated cirrhosis	**50.0%* (13/26)**	**13**	**26**
Partial response	GT1a	F0-F1	Mild	62.2%^	2.31#	3.71+
Partial response	GT1a	F2-F3	Moderate	65.8%^	8.38#	12.73+
Partial response	GT1a	F4	Compensated cirrhosis	24.1%^	2.31#	9.55+
Partial response	GT1b	F0-F4	Mild, moderate, compensated cirrhosis	**68.2%* (15/22)**	**15**	**22**
Partial response	GT1b	F0-F1	Mild	80.4%^	2.53#	3.14+
Partial response	GT1b	F2-F3	Moderate	84.0%^	9.05#	10.78+
Partial response	GT1b	F4	Compensated cirrhosis	42.3%^	3.42#	8.08+
Prior Relapse	GT1	F0-F4	Mild, moderate, compensated cirrhosis	**83.4%*** (**121/145**)	**121**	**145**
Prior Relapse	GT1	F0-F1	Mild	**85.3%* (29/34)**	**29**	**34**
Prior Relapse	GT1	F2-F3	Moderate	**83.1%* (69/83)**	**69**	**83**
Prior Relapse	GT1	F4	Compensated cirrhosis	**82.1%* (23/28)**	**23**	**28**
Prior Relapse	GT1a	F0-F4	Mild, moderate, compensated cirrhosis	**80.0%* (52/65)**	**52**	**65**
Prior Relapse	GT1a	F0-F1	Mild	81.8%^	12.47#	15.24+
Prior Relapse	GT1a	F2-F3	Moderate	79.7%^	29.65#	37.21+
Prior Relapse	GT1a	F4	Compensated cirrhosis	78.7%^	9.88#	12.55+
Prior Relapse	GT1b	F0-F4	Mild, moderate, compensated cirrhosis	**87.0%* (67/77)**	**67**	**77**
Prior Relapse	GT1b	F0-F1	Mild	88.9%^	16.04#	18.06+
Prior Relapse	GT1b	F2-F3	Moderate	86.7%^	38.21#	44.08+
Prior Relapse	GT1b	F4	Compensated cirrhosis	85.7%^	12.74#	14.87+

Data taken directly from clinical trial publication in boldface font.

^SVR #number of patients with SVR (n) +The imputed total number of patients in a subgroup (N) all imputed (methodology described previously)
Source:
*Tables 42-44 in CHMP Assessment Report: Incivo Procedure No.: EMEA/H/C/002313 European Medicines Agency Jul 2011.[92]

166 of the 266 patients enrolled in T12PR48 completed treatment. Of those who discontinued treatment, 39 patients (14.7% of enrolled patients) discontinued treatment due to an adverse event. Consolidated adverse event results were reported for all patients, and our model assumes that adverse event profiles are the same across all fibrosis stages and modality of prior non-response. The Table 91 below summarises the adverse event findings from T12PR48 that were uniformly applied in our model to all subgroups of patients.

Table 91: Selected adverse events for telaprevir + PR in treatment-experienced, genotype 1 patients: REALIZE trial, T12PR48 arm

Event	Genotype	Fibrosis Stages	n (%)	N
Anaemia	GT1	Mild, moderate, compensated cirrhosis	**79**^^ (29.7)	266
Rash	GT1	Mild, moderate, compensated cirrhosis	**99**^^ (37.2)	266
Depression	GT1	Mild, moderate, compensated cirrhosis	**24**^^ (9.02)	266
Neutropenia	GT1	Mild, moderate, compensated cirrhosis	**34.29**^* (12.9)	266
Thrombocytopenia	GT1	Mild, moderate, compensated cirrhosis	**11.76*** (4.42)	266

Adverse events reported in Zeuzem et al., 2011 and Kauffman et al., 2011 in bold font.
Combined Grade 3-4 Neutropenia and Grade 3-4 Thrombocytopenia reported in Kauffman et al., 2011 for REALIZE T12PR48 and lead-in T12PR48 arms. We compute the weighted number of AE based on sample sizes, rounded to 2 decimal places:
N_Neutropenia= (39+4)*[194/(194+197)] + (20+5)*[72/(72+67)] = 34.29;
N_Thrombocytopenia= (6+1)*[194/(194+197)] + (15+1)*[72/(72+67)] = 11.76.
Sources:
^Table 3 in Zeuzem et al. Telaprevir for Retreatment of HCV Infection. *N Engl J Med.* 2011; 364:2417-2428.
^^Supplementary Table 2 in Zeuzem et al., 2011.
*Table 5 in Kauffman et al.[93]

PR in GT1, treatment-experienced patients (IFN-eligible): REALIZE trial

The control group (PR48) of the REALIZE trial received PR for 48 weeks. This group had 132 patients with GT1 HCV infection, 45% of whom had fibrosis (METAVIR) scores F3-F4. There was also an equal number (n=59) of GT1a and 1b patients. In the model, we use the observed SVR24 of treatment-experienced patients in the PR48 group of REALIZE trial. Dosing strength and duration of PR are similar to that of PR in the T12PR48 group. Stopping rules were applied to all patients in PR48, the details of which may be found in Zeuzem et al. (2011).[91] In the disease model, we make the same assumptions and apply the same computational rules for PR48 as we did for T12PR48. Our results are tabulated below.

Table 92: Reported and imputed SVR rates for PR in GT1 patients from the PR48 arm of the REALIZE trial, by type of prior response and fibrosis stage

Treatment Status	GT/ SubGT	Fibrosis Stage (REALIZE)	Fibrosis Stage (model)	Reported/ Imputed SVR	n	N
Null response	GT1	F0-F4	Mild, moderate, compensated cirrhosis	**5.4%*** (**2/37**)	**2**	**37**
Null response	GT1	F0-F1	Mild	**0.0%* (0/5)**	**0**	**5**
	GT1	F2-F3	Moderate	**4.5%* (1/22)**	**1**	**22**
Null response	GT1	F4	Compensated cirrhosis	**10.0%*** (**1/10**)	**1**	**10**
Null response	GT1a	F0-F4	Mild, moderate, compensated cirrhosis	**5.9%* (1/17)**	**1**	**17**
Null response	GT1a	F0-F1	Mild	0.0%^	0.00 #	2.30+
	GT1a	F2-F3	Moderate	4.9%^	0.50 #	10.11 +
Null response	GT1a	F4	Compensated cirrhosis	10.9%^	0.50 #	4.59+
Null response	GT1b	F0-F4	Mild, moderate, compensated cirrhosis	**5.0%* (1/20)**	**1**	**20**
Null response	GT1b	F0-F1	Mild	0.0%^	0.00 #	2.70+
	GT1b	F2-F3	Moderate	4.2%^	0.50 #	11.89 +
Null response	GT1b	F4	Compensated cirrhosis	9.3%^	0.50 #	5.41+
Partial response	GT1	F0-F4	Mild, moderate, compensated cirrhosis	**14.8%*** (**4/27**)	**4**	**27**
Partial response	GT1	F0-F1	Mild	**0.0%* (0/10)**	**0**	**10**
	GT1	F2-F3	Moderate	**25.0%* (3/12)**	**3**	**12**
Partial response	GT1	F4	Compensated cirrhosis	**20.0%* (1/5)**	**1**	**5**
Partial response	GT1a	F0-F4	Mild, moderate, compensated cirrhosis	**18.8%* (3/16)**	**3**	**16**
Partial response	GT1a	F0-F1	Mild	0.0%^	0.00 #	5.93+
	GT1a	F2-F3	Moderate	31.6%^	2.25 #	7.11+
Partial response	GT1a	F4	Compensated cirrhosis	25.3%^	0.75 #	2.96+

Partial response	GT1b	F0-F4	Mild, moderate, compensated cirrhosis	**10.0%* (1/10)**	**1**	**10**
Partial response	GT1b	F0-F1	Mild	0.0%^	0.00 #	3.70+
	GT1b	F2-F3	Moderate	16.9%^	0.75 #	4.44+
Partial response	GT1b	F4	Compensated cirrhosis	13.5%^	0.25 #	1.85+
Prior Relapse	GT1	F0-F4	Mild, moderate, compensated cirrhosis	**23.5%* (16/68)**	**16**	**68**
Prior Relapse	GT1	F0-F1	Mild	**35.0%* (7/20)**	**7**	**20**
Prior Relapse	GT1	F2-F3	Moderate	**21.2%* (7/33)**	**7**	**33**
Prior Relapse	GT1	F4	Compensated cirrhosis	**13.3%* (2/15)**	**2**	**15**
Prior Relapse	GT1a	F0-F4	Mild, moderate, compensated cirrhosis	**29.4%* (10/34)**	**10**	**34**
Prior Relapse	GT1a	F0-F1	Mild	40.9%^	4.09 #	10.00 +
Prior Relapse	GT1a	F2-F3	Moderate	27.1%^	4.47 #	16.50 +
Prior Relapse	GT1a	F4	Compensated cirrhosis	19.2%^	1.44 #	7.50+
Prior Relapse	GT1b	F0-F4	Mild, moderate, compensated cirrhosis	**19.4%* (6/31)**	**6**	**31**
Prior Relapse	GT1b	F0-F1	Mild	30.8%^	2.81 #	9.12+
Prior Relapse	GT1b	F2-F3	Moderate	17.0%^	2.56 #	15.04 +
Prior Relapse	GT1b	F4	Compensated cirrhosis	9.2%^	0.63 #	6.84+

Data taken directly from clinical trial publication in boldface font.

^SVR imputed using previously described methodology. We assume the decrement in SVR rates from mild/moderate fibrosis to compensated cirrhosis are the same for GT1a and GT1b patients as that for Gt1 patients..

#The imputed number of patients with SVR (n

+The imputed total number of patients in a subgroup (N)

Source:

*Tables 42-44 in CHMP Assessment Report: Incivo (telaprevir)[92]

Fifty of the 132 patients (38%) enrolled in the PR48 arm completed treatment (Figure 1 in Zeuzem et al. 2011). Of those who discontinued treatment, 4 patients (3.03% of enrolled patients) discontinued treatment due to an AE (Table 3 in Zeuzem et al.) Consolidated AE results were reported for all patients, and our model assumes that AE profiles are the same across fibrosis status, cirrhosis and type of prior response.

The table below summarises the AE findings from the PR48 arm that were uniformly applied in our model to all subgroups of patients.

Table 93: **Selected AE rates for PR in GT1, treatment-experienced patients from the PR48 arm of the REALIZE trial**

Event	GT/ SubGT	Fibrosis Stage	n (%)	N
Anaemia	GT1	Mild, moderate, compensated cirrhosis	**20**^^ (15.2)	**132**
Rash	GT1	Mild, moderate, compensated cirrhosis	**25**^^ (18.9)	**132**
Depression	GT1	Mild, moderate, compensated cirrhosis	**19**^^ (14.4)	**132**
Neutropenia	GT1	Mild, moderate, compensated cirrhosis	**19**^* (14.4)	**132**
Thrombocytopenia	GT1	Mild, moderate, compensated cirrhosis	**4**** (3.0)	**132**

AE = adverse event; GT = genotype; PR = peg-IFN and ribavirin.
Data taken directly from clinical trial publication in **boldface** font.
Grade 3-4 Neutropenia and Thrombocytopenia reported in Kauffman et al. (2011).
Sources:
^Table 3 in Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011;364(25):2417-28.
^^Supplementary Table 2 in Zeuzem et al. (2011).
*Table 5 in Kauffman et al.[86]

Boceprevir (BOC) + PR in GT1, prior partial response and prior relapse (IFN-eligible) patients: RESPOND-2 trial

RESPOND-2 was a phase 3 double blind, placebo controlled study in treatment-experienced genotype 1 patients[94], categorised as non-response (i.e., a decrease in the HCV RNA level of at least 2 log10 IU per millilitre by week 12 but detectable HCV RNA level during the therapy period) or relapse (i.e., an undetectable HCV RNA level at the end of treatment, without subsequent attainment of a SVR). Note that the definition of non-response in RESPOND-2 corresponds to a definition of partial response in the telaprevir and AbbVie Regimen trials. Therefore for the modelling purposes, our interpretation is that the prior non-responder data are representative of prior partial responders. Further, RESPOND-2 trial excluded patients with prior null response to from this Phase 3 study hence no data exist for patients with prior null response to PR. Therefore, the comparison of 3D regimen with BOC+PR was only possible in partial responders and prior relapsers (which we present) and was not possible in treatment-experienced patients overall as AbbVie's model is structured in such way that it requires the availability of data in all three subgroups of patients (partial, relapse and null responders) to generate results for overall treatment experienced patients. This is the limitation given that the model was structured in this way to be able to explore results in discrete subgroups requested by NICE in the final scope.

All patients received a 4-week lead-in phase with peginterferon-ribavirin (PR). The response-guided treatment regimen (RGT) enrolled 162 patients: those with undetectable HCV RNA through weeks 8 and 12 received 32 weeks of boceprevir (BOC) + PR for a total treatment duration of 36 weeks, while those with detectable HCV RNA at week 8 but undetectable at week 12 received PR for an additional 12 weeks (total treatment duration of 48 weeks). In the fixed duration treatment (FDT) group, following 4-weeks lead-in with PR 161 patients were administered BOC + PR for a total of 44 weeks. Patients received peginterferon alfa-2b subcutaneously at a dose of 1.5 µg per kilogram once weekly and weight-based ribavirin orally at a total dose between 600 to 1400 mg per day. Boceprevir was taken orally at a dose of 800

mg every 7 to 9 hours. Primary efficacy endpoint was SVR24. The results were published in Bacon et al., 2011.[94]

Although 12 more patients achieved SVR in the FDT group than the RGT group, the resulting odds ratio (FDT vs. RGT) had a confidence interval of 0.9 to 2.2, which implies that the SVR rates between FDT and RGT groups are not statistically different. Post hoc exploratory analyses revealed that the difference appeared to be driven by patients with cirrhosis at baseline: 18% of patients with cirrhosis in the RGT group had undetectable HCV RNA level at week 8, compared with 73% in the FDT group. Moreover, given that the cost of the FDT regimen is significantly higher than the cost of the RGT regimen, we apply results from the RGT group to the model.

Fifty-eight percent of patients had sub-genotype 1a in the RGT group (Table 1 in Bacon et al). The distribution by fibrosis status was as follows: 58% of patients had mild fibrosis, 30% had moderate fibrosis, and 11% had compensated cirrhosis (Supplementary Table S2 in Bacon et al; tabulated from patients with non-missing values of Metavir fibrosis scores). SVR rates were presented by Metavir fibrosis scores, type of prior non-response, and sub-genotype. We consolidate the results by Metavir fibrosis scores to align with our model, namely: F0-F1: mild cirrhosis, F2-F3: moderate cirrhosis, F4: compensated cirrhosis. Table 94 below consolidates the published findings.

Table 94: Reported SVR for boceprevir + PR in treatment-experienced, genotype 1 patients: RESPOND-2 trial, RGT arm

Treatment Status	Treatment Arm	Genotype/ Sub-genotype	Fibrosis Stages[#] (RESPOND-2)	Reported SVR	n	N
Treatment-experienced	RGT	GT1	F0-F4	**58.6%*** (**95/162**)	**95**	**162**
Partial response	RGT	GT1	F0-F4	**40.4%* (23/57)**	**23**	**57**
Prior Relapse	RGT	GT1	F0-F4	**68.6%* (72/105)**	**72**	**105**
Treatment-experienced	RGT	GT1	F0-F1	**66.7%**** (**58/87**)	**58**	**87**
Treatment-experienced	RGT	GT1	F2-F3	**60.0%**** (**27/45**)	**27**	**45**
Treatment-experienced	RGT	GT1	F4	**35.3%** (6/17)**	**6**	**17**
Treatment-experienced	RGT	GT1a	F0-F4	**50.0%* (37/74)**	**37**	**74**
Treatment-experienced	RGT	GT1b	F0-F4	**65.3%* (49/75)**	**49**	**75**

Data taken directly from Bacon et al., 2011 are in bold font;
[#] We consolidate the results by Metavir fibrosis scores to align with our model, namely: F0-F1: mild cirrhosis, F2-F3: moderate cirrhosis, F4: compensated cirrhosis.
Sources:
*Source: Figure 3 in Bacon et al. 2011;364:1207-1217.[94]
** Supplementary Table S2 in Bacon et al., 2011.

We observe that as fibrosis progresses from mild to moderate, SVR falls by 6.7%. As moderate fibrosis progresses to compensated cirrhosis, SVR decreases by a further 24.7%. We impute the SVR values for partial response and prior relapse patients by assuming that the decrements in SVR rates are similar regardless of modality of non-response, namely, SVR falls by 6.7% from mild to moderate, and 24.7% from moderate to compensated cirrhosis. Therefore assuming the SVR of a partial response patient with compensated cirrhosis is given by SVRcc,partial, it can be calculated as: 40.4% = 0.58 * (SVRcc,partial + 6.7% + 24.7%) + (0.30) * (SVRcc,partial + 24.7%) + 0.11 * SVRcc,partial. Thus, SVRcc,partial = 14.6%. The table below tabulates results for partial response and relapse patients.

Table 95: Reported and imputed SVR for boceprevir + PR in treatment-experienced patients, for partial responders and relapsers, by fibrosis stages: RESPOND-2 trial, RGT arm

Treatment Status	Genotype/Sub-genotype	Fibrosis Stages (RESPOND-2)	Fibrosis Stages (model)	Reported/Imputed SVR	n	N
Partial response	GT1	F0-F4	Mild, moderate, compensated cirrhosis	**40.4%* (23/57)**	**23**	**57**
Partial response	GT1	F0-F1	Mild	45.9%^	15.29#	33.28+
Partial response	GT1	F2-F3	Moderate	39.3%^	6.76#	17.21+
Partial response	GT1	F4	Compensated cirrhosis	14.6%^	0.95#	6.50+
Prior Relapse	GT1	F0-F4	Mild, moderate, compensated cirrhosis	**68.6%* (72/105)**	**72**	**105**
Prior Relapse	GT1	F0-F1	Mild	74.2%^	45.47#	61.31+
Prior Relapse	GT1	F2-F3	Moderate	67.5%^	21.40#	31.71+
Prior Relapse	GT1	F4	Compensated cirrhosis	42.8%^	5.13#	11.98+

Data taken directly from Bacon et al., 2011 are in bold font;
^SVR imputed; see text.
#The imputed number of patients with SVR (n).
+The imputed total number of patients in a subgroup (N) is computed using the weighted average of patients by fibrosis status. We further assume that the distributions of fibrosis in partial response and relapse patients are the same as the entire cohort of treatment-experienced patients, namely 58% mild, 30% moderate, 11% compensated cirrhosis. Results are reported to 2 decimal places.
Source:
*Figure 3 in Bacon et al. 2011

Of the 162 patients enrolled in the RGT arm, 13 (8.02%) discontinued treatment due to an adverse event (Table 1 in Bacon et al., 2011). Consolidated adverse event results were reported for all patients and we assume in our model that adverse event profiles are the same across fibrosis status and type of prior non-response. Table 96 below summarises the adverse event findings for the RGT arm that were uniformly applied in our model to all subgroups of patients.

Table 96: Selected adverse events for boceprevir + PR in treatment-experienced, genotype 1 patients: RESPOND-2 trial

Event	Genotype	Fibrosis Stages	n (%)	N
Anaemia	GT1	F0-F4	**70**[^] (43.2)	162
Rash	GT1	F0-F4	**27**[^] (16.7)	162
Depression	GT1	F0-F4	**20**[^] (12.4)	162
Neutropenia	GT1	F0-F4	**40**[*] (24.7)	162
Thrombocytopenia	GT1	F0-F4	0**	162

Adverse events in bold font are reported in Bacon et al., 2011.
Only Grade 3-4 (<1x10^9/L) Neutropenia reported.
**Grade 3-4 (<50 x 10^9/L) Thrombocytopenia not reported and assumed to be zero.
Sources:
*Table 2 in Bacon et al. 2011
[^]Supplementary Table S5 in Bacon et al., 2011.

Sofosbuvir (SOF) + PR in GT4, treatment-naïve (IFN-eligible) patients: NEUTRINO trial

The NEUTRINO trial was described earlier in the section.[84] We focus here on the GT4 treatment-naïve patients without cirrhosis. The table below shows SVR rates taken from the NICE sofosbuvir STA (currently ongoing at time of submission). In GT 4, 5, 6 patients, all 33 patients without cirrhosis achieved SVR (Table 55 in SOF+PR STA); we also know from SOF+PR FDA label that 27/28 GT4 patients achieved SVR (96.4%). Therefore given SVR was 100% in non-cirrhotic GT1,4,5,6 and 96.4% in the overall GT4 patients suggests that that one patient who didn't achieve SVR was most likely cirrhotic. Therefore we can safely assume that GT4 non-cirrhotic patients achieved 100% SVR. Since we are only interested in GT4 patients without cirrhosis, it is sufficient to know that SVR is 100% in this patient segment.
Table **97** below shows our results.

Table 97: Reported/inferred SVR rates for SOF + PR in treatment-naïve, GT4 patients from the NEUTRINO trial

Treatment Status	GT/ SubGT	Fibrosis Stage	Reported/Inferred SVR	n	N
Naïve	GT4,5, 6	Mild, moderate, compensated cirrhosis	**97.1%** (**34/35**)	**34**	**35**
Naïve	GT4,5, 6	Mild, moderate	**100.0%** (**33/33**)	**33**	**33**
Naïve	GT4	Mild, moderate, compensated cirrhosis	**96.4%** (**27/28**)	**27**	**28**
Naïve	GT5	Mild, moderate, compensated cirrhosis	**100.0%** (**1/1**)	**1**	**1**
Naïve	GT6	Mild, moderate, compensated cirrhosis	**100.0%** (**6/6**)	**6**	**6**
Naïve	GT4	Mild, moderate	100.0%	27	27

Data taken directly from SOF STA in **boldface** font.
Sources:
Single technology appraisal (STA) for Sofosbuvir - Chronic hepatitis C *National Institute for Health and Care Excellence* March 2014.[95]

NEUTRINO reported combined discontinuation and AE rates across patients with different genotypes treated with SOF + PR for 12 weeks. Consistent with model assumptions, we apply the AE rates for the GT1, 4, 5, 6 patients of NEUTRINO to GT4 patients, just as it was done for GT1 patients.

PR in GT4, treatment-naïve (IFN-eligible) patients

The introduction of PR improved the efficacy of treatment in HCV GT4 significantly. Studies have shown that SVR rates are higher than those achieved for GT1 patients treated with PR.[96] In a meta-analysis of 5 randomised control trials enrolling 386 patients with GT4, Aljumah and Murad (2013) found that SVR rate was significantly higher in the peg-IFN-alpha-2a (peg-IFN-α-2a) group than in the peg-IFN-α-2b group (P = 0.02).[97] As such, we apply peg-IFN-α-2a as the standard of care for GT4 patients in our model.

In a prospective, randomised, open-label, parallel-group clinical trial, 109 GT4 treatment-naïve patients were randomly assigned to receive 180 µg of peg-IFN-α-2a subcutaneously once weekly plus oral WBR for 48 weeks (Kamal et al. (2011)).[98] The primary endpoint was SVR measured 24 weeks after the completion of treatment. Table 1 reported median liver histology of 1.0, measured by the Ishak fibrosis score; with a range between 0 and 4. This range corresponds to a fibrosis (METAVIR) score of F0-F3 (refer to Figure 1 of Shiha and Zalata).[99] Kamal et al. (2011) did not breakdown SVR by fibrosis subgroups, and we therefore assume in the model that SVR for mild (F0-F1) and moderate (F2-F3) patients are the same. The table below shows the results.

Table 98: Reported SVR rates for peg-IFN-α-2a and ribavirin in GT4, treatment-naïve patients: Kamal et al. (2011)

Treatment Status	GT	Ishak Score	Fibrosis Stage (model)	Reported SVR	n	N
Naïve	GT4	0-4	Mild, moderate	**70.6%*** (**77/109**)	**77**	**109**

Source:
*Table 2 in Kamal et al., 2011[98]

A total of two patients discontinued treatment: one enrolled patient (0.92%) discontinued treatment due to anaemia and neutropenia; while another patient was non-adherent (Figure 1 in Kamal et al., 2011). Given that the five modelled AEs were not consistently reported in Kamal et al. (2011), we extend our assumption that AEs are treatment and duration specific but not genotype dependent here, to extrapolate AEs from GT1, treatment-naïve patients (i.e., the PR arm of ADVANCE).

In scenario analysis, we apply SVR rates from Yee et al. (2014): 61.3% (= 587/958) in patients with mild and moderate fibrosis (Supplemental Figure 4a, which focused only on studies that used METAVIR scoring). In Yee et al. (2014), mild fibrosis is categorised as F0-F2, whereas severe fibrosis is categorised as F3-F4; thus applying an SVR of 61.3% to mild and moderate patients (F0-F3) is conservative.[100]

PR in GT4, treatment-experienced (IFN-eligible) patients

There is limited data on the efficacy of PR in GT4, treatment-experienced patients. EPIC3[101] was a prospective, international, multi-centre, open-label study evaluated efficacy and safety of peg-IFN alfa-2b (1.5 microg/kg/week) plus WBR in 2333 chronic HCV-infected GT1, 2, 3, and 4 patients with METAVIR score F2-F4 whose previous IFN/R therapy failed. Patients with undetectable HCV-RNA at treatment week (TW) 12 received 48 weeks of therapy; patients with detectable HCV-RNA at TW12 could enter maintenance studies at TW18; 188 patients with low/detectable HCV-RNA at TW12 continued therapy at the investigator's request. Table 2 of Poynard et al. (2009) showed that SVR in GT4 patients was 28.4% (19/67). However, this rate is likely to be conservative as research has shown that peg-IFN-α-2b is less efficacious in GT4 patients than peg-IFN-α-2a; moreover, the trial only recruited patients with moderate fibrosis or compensated cirrhosis – extending the same SVR to patients with mild fibrosis will further bias its efficacy negatively. Thus we decide against using this data to compare against the AbbVie Regimen, as it would bias results in favour of the intervention in GT4, treatment-experienced patients without cirrhosis.

No treatment in GT1 and GT4, IFN-unsuitable patients

Finally, we assume in the model that with no treatment, GT1 and GT4 patients across all levels of fibrosis have a 0% SVR rate. We further assume that with no treatment, no treatment-related AEs occur. This is consistent with assumptions made in studies that included a 'no antiviral treatment' placebo arm, and summarised in Brady et al. (2007).[102] In the model, we compare the AbbVie Regimen specifically to No Treatment in IFN-unsuitable, GT1, treatment-naïve and -experienced patients, as well as to GT4 treatment-naïve and -experienced patients (IFN-unsuitable) patients without cirrhosis.

Treatment duration

Mean treatment durations are derived from the pivotal trials for all therapies and as such allow for per patient drug and treatment monitoring costs to be appropriately estimated. Thus, in order to obtain an accurate estimate for the duration of therapy, we take into account patients that drop out during trials. This method allows us to derive 'trial-based' treatment duration and it may be argued that it also reflects 'real world' adherence to some degree. For more details on how 'trial-based' treatment durations have been estimated, please refer to the section 7.5 of the submission.

Health Related Quality of Life

To take account of adverse events associated with antiviral therapy on patients' HRQoL, health state utilities are reduced during the year in which treatment occurs. Treatment related utility decrements for AbbVie's Regimens are based on their respective clinical trials where the treatment related disutility has been calculated as the difference between the baseline utility of patients and the end-of-treatment (EOT) week 12 utility. For all comparator therapies, treatment-related utility decrements have been sourced from the available published literature.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition

matrix, details of the transformation of clinical outcomes or other details here.

We obtain non-treatment-specific data, including those to inform the progression of liver disease through the HCV natural history model, directly from available published sources. These sources include previous UK economic evaluations such as Hartwell et al. (2011) [51], Grishchenko et al. (2009),[66] Shepherd et al. (2007) [57], and Wright et al. (2006). [70]

Non-treatment-specific clinical data

In Section 7.2, we describe the model structure, noting its alignment with previous UK economic evaluations. In the base case, we apply transitional probabilities from these sources, as data for them were derived from representative UK-specific samples. The Table 99 below describes the non-treatment-specific transitional probabilities that are used in the model for base case analysis. We vary these individually in deterministic sensitivity analysis.

Table 99: Non-treatment-specific transitional probabilities used in model base case analysis

Transitional Probability	Base Case Value	Source
Fibrosis progression		
Mild to Moderate	0.025	Wright et al. (2006); Grieve et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)
Moderate to CC	0.037	Wright et al. (2006); Grieve et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)
Non-fibrosis progression		
Recovered, no HCV, History of Severe Fibrosis (CC) to HCC	0.012	Cardoso et al. (2010)
CC to DCC	0.039	Fattovich et al. (1997); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)
CC to HCC (First Year)	0.014	Fattovich et al. (1997); Wright et al. (2006); Grieve et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)
DCC to HCC (First Year)	0.014	Fattovich et al. (1997); Wright et al. (2006); Grieve et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)
Liver Transplant		
DCC to Liver Transplant (First Year)	0.020	Grieve et al. (2006); Wright et al. (2006); Shepherd et al. (2007); Siebert et al. (2003) Hartwell et al. (2011)
HCC to Liver Transplant (First Year)	0.020	Wright et al. (2006); Expert opinion; implied in Hartwell et al. (2011)
Liver-related Mortality		
DCC to Liver Death	0.130	Fattovich et al. (1997); Wright et al. (2006); Grieve et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)

Liver Transplant to Liver Death	0.150	Hartwell et al. (2011); Grieve et al. (2006)
After Liver Transplant to Liver Death	0.057	Shepherd et al. (2007); Hartwell et al. (2011); Bennett et al. (1997)
HCC First Year to Liver Death	0.430	Fattovich et al. (1997); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)
HCC Subsequent Year to Liver Death	0.430	Fattovich et al. (1997); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)
Viral reinfection	0.010	Expert opinion

CC = compensated cirrhosis; HCC = hepatocellular carcinoma; DCC = decompensated cirrhosis.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

There is no evidence to suggest that transition probabilities in chronic hepatitis C should vary over time which is consistent with previous cost-effectiveness analyses.

For transitional probabilities (TPs) related to fibrosis progression, we reference Hartwell et al. (2011)[51] in the base case analysis. These TPs are age non-varying. Previous economic evaluations such as Wright et al. (2006)[70] and Shepherd et al. (2007)[57] also used the same approach. Transition probabilities as reported in Grishchenko et al. (2009) [66] are being explored in scenario analysis. Grishchenko et al. (2009) used data from the Trent HCV database in the UK to derive transitional probabilities for early disease, for progression to compensated cirrhosis that varied by patient age at treatment.

A NICE Evidence Review Group (ERG) previously criticised the interpretation that these transitional probabilities represent time-varying transitional probabilities by patient age instead of only age at treatment.[103] Based on the ERG's comment, we modified the application of these transitional probabilities to vary by age at treatment and not by time. In other words, the "age-adjustment" is only relevant at the start of treatment, with transitional probabilities remaining constant thereafter. For instance, a person aged 40-49 has the same probability in model cycle 1 as in model cycle 10 for transitioning to a worse fibrosis stage, irrespective of their chronological age increasing. Transitional probabilities related to treatment efficacy occur in the first model cycle and also do not vary over time.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No, as the final outcome measured is SVR, a virologic cure.

7.3.5 Clinical experts assessed the applicability of values available or estimated any values, the following details are provided:

The model structure and inputs were validated by clinical experts, an epidemiologist, health economist and specialist viral-hepatitis pharmacist during an advisory board held in England, which offered a good breath of opinions representative of clinical practice in the UK. Clinical experts were selected on the basis of their knowledge and expertise in treating hepatitis and thus provided recommendations for clinical assumptions within the model pertaining to model health states, transition probabilities, adverse events associated with therapies, anticipated monitoring requirements of new DAAs and rates of viral re-infections. An independent epidemiologist and health economist provided expert opinion on the natural history and cost-effectiveness aspects of the model. Data summarised below were gathered and subsequently used to inform our model assumptions:

The external experts approached have previously attended advisory boards for AbbVie as well as other manufacturers of HCV therapies including but not limited to Gilead Sciences and Janssen.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 100 and
Table **101** below show non-treatment specific and treatment specific variables included in the model. The values tested in scenario analysis are captured in Section 7.6.1; details of the ranges varied in sensitivity analysis, namely DSA and PSA, are provided in Section 7.6.2 and 7.6.3 respectively.

Table 100: **Summary of non-treatment-specific variables included in the cost-effectiveness model**

Variable	Base Case Value	Source	Reference to section in submission
Time horizon	70 years	The time horizon is essentially a lifetime time horizon, consistent with Hartwell et al. (2011).	7.2.6, 7.6.1
Baseline characteristics			
Proportion of GT1	68.8%	Harris et. al. (1999)[72]	7.2.6, 7.6.1

patients who are GT1a			
Distribution of patients by prior non-response			
Null response	30.0%	NICE Simeprevir STA, 2014[104]	7.2.6
Partial response	30.0%	NICE Simeprevir STA, 2014[104]	7.2.6
Prior relapse	40.0%	NICE Simeprevir STA, 2014[104]	7.2.6
GT1 & GT4 treatment-naïve			
Initial Fibrosis Distribution[51]			
Mild	46.0%	Hartwell et al. (2011)	7.2.6, 7.6.1
Moderate	44.0%	Hartwell et al. (2011)	7.2.6, 7.6.1
CC (Chronic HCV)	10.0%	Hartwell et al. (2011)	7.2.6, 7.6.1
Age (in Years)	40	Hartwell et al. (2011)	7.2.6, 7.6.1
Male	70.0%	Hartwell et al. (2011)	7.2.6, 7.6.1
GT1 treatment-experienced			
Initial Fibrosis Distribution[51]			
Mild	33.0%	Hartwell et al. (2011)	7.2.6, 7.6.1
Moderate	35.0%	Hartwell et al. (2011)	7.2.6, 7.6.1
CC (Chronic HCV)	32.0%	Hartwell et al. (2011)	7.2.6, 7.6.1
Age (in Years)	45	Hartwell et al. (2011)	7.2.6, 7.6.1
Male	70.0%	Hartwell et al. (2011)	7.2.6, 7.6.1
Transitional probabilities			
Fibrosis Progression[51,57,70,105]			
Base case			
Mild to Moderate	0.025	Wright et al. (2006); Grieve et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.2.5, 7.3.2, 7.6.2, 7.6.3
Moderate to CC	0.037	Wright et al. (2006); Grieve et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.2.5, 7.3.2, 7.6.2, 7.6.3
Sensitivity[66]			
Mild to Moderate, Age at treatment			
30-39 Years	0.015	Grishchenko et al. (2009)	7.2.5, 7.3.3, 7.6.1
40-49 Years	0.023	Grishchenko et al. (2009)	7.2.5, 7.3.3, 7.6.1
50-59 Years	0.035	Grishchenko et al. (2009)	7.2.5, 7.3.3, 7.6.1
Moderate to CC, Age at treatment			
30-39 Years	0.021	Grishchenko et al. (2009)	7.2.5, 7.3.3, 7.6.1
40-49 Years	0.032	Grishchenko et al. (2009)	7.2.5, 7.3.3, 7.6.1

50-59 Years	0.048	Grishchenko et al. (2009)	7.2.5, 7.3.3, 7.6.1
Non-Fibrosis Progression			
Recovered, no HCV, History of Severe Fibrosis (CC) to HCC	0.012	Cardoso et al. (2010)[82]	7.2.5, 7.3.2, 7.6.2, 7.6.3
CC to DCC[65,51]	0.039	Fattovich et al. (1997); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.2.5, 7.3.2, 7.6.2, 7.6.3
CC to HCC (First Year)[65,51]	0.014	Fattovich et al. (1997); Wright et al. (2006); Grieve et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.2.5, 7.3.2, 7.6.2, 7.6.3
DCC to HCC (First Year)[65,51]	0.014	Fattovich et al. (1997); Wright et al. (2006); Grieve et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.2.5, 7.3.2, 7.6.2, 7.6.3
Liver Transplant			
DCC to Liver Transplant (First Year)[51,57]	0.020	Grieve et al. (2006); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.2.5, 7.3.2
HCC to Liver Transplant (First Year)[51]	0.020	Wright et al. (2006); Expert opinion; implied in Hartwell et al. (2011)	7.2.5, 7.3.2
Liver-related Mortality			
DCC to Liver Death	0.130	Fattovich et al. (1997); Wright et al. (2006); Grieve et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.2.5, 7.3.2, 7.6.2, 7.6.3
Liver Transplant to Liver Death	0.150	Hartwell et al. (2011); Grieve et al. (2006)	7.2.5, 7.3.2
After Liver Transplant to Liver Death	0.057	Shepherd et al. (2007); Hartwell et al. (2011); Bennett et al. (1997)	7.2.5, 7.3.2
HCC First Year to Liver Death	0.430	Fattovich et al. (1997); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.2.5, 7.3.2, 7.6.2, 7.6.3
HCC Subsequent Year to Liver Death	0.430	Fattovich et al. (1997); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.2.5, 7.3.2, 7.6.2, 7.6.3
Viral Reinfection	0.010	Expert opinion	7.2.5, 7.3.2, 7.6.2, 7.6.3
Background age- and gender-adjusted probability of death, annual	variable	ONS, National life tables for the UK, based on data for the years 2010-2012	7.2.3
Unit costs (2013/14)			
Health state direct costs			
Mild	£160	Hartwell et al. (2011)	7.5.1, 7.5.6, 7.6.2, 7.6.3
Moderate	£589	Backx et al. (2014)[106]	7.5.1, 7.5.6, 7.6.2, 7.6.3
CC (Chronic HCV)	£914	Backx et al. (2014)	7.5.1, 7.5.6,

			7.6.2, 7.6.3
Recovered, no HCV, history of mild fibrosis	£58	Backx et al. (2014)	7.5.1, 7.5.6, 7.6.2, 7.6.3
Recovered, no HCV, history of moderate fibrosis	£58	Backx et al. (2014)	7.5.1, 7.5.6, 7.6.2, 7.6.3
Recovered, no HCV, history of severe fibrosis (CC)	£586	Backx et al. (2014)	7.5.1, 7.5.6, 7.6.2, 7.6.3
DCC	£12,333	Hartwell et al. (2011)[51]	7.5.1, 7.5.6, 7.6.2, 7.6.3
HCC (first year)	£10,990	Hartwell et al. (2011)	7.5.1, 7.5.6, 7.6.2, 7.6.3
HCC (subsequent year)	£10,990	Hartwell et al. (2011)	7.5.1, 7.5.6, 7.6.2, 7.6.3
Liver transplant (first year)	£49,749	Hartwell et al. (2011)	7.5.1, 7.5.6, 7.6.2, 7.6.3
Liver transplant (subsequent year)	£1,873	Hartwell et al. (2011)	7.5.1, 7.5.6, 7.6.2, 7.6.3
Treatment-related adverse event			
Anaemia	£482	Thorlund et al. (2012)[107]	7.5.1, 7.5.6, 7.6.2, 7.6.3
Rash	£160	Thorlund et al. (2012)	7.5.1, 7.5.6, 7.6.2, 7.6.3
Depression	£398	Thorlund et al. (2012)	7.5.1, 7.5.6, 7.6.2, 7.6.3
Neutropenia	£942	NICE Sofosbuvir STA, 2014[95]	7.5.1, 7.5.6, 7.6.2, 7.6.3
Thrombocytopenia	£841	NICE Sofosbuvir STA, 2014[95]	7.5.1, 7.5.6, 7.6.2, 7.6.3
Health state-related utilities			
Mild	0.77	Grieve et al. (2006); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.4.2, 7.4.9, 7.6.2, 7.6.3
Moderate	0.66	Grieve et al. (2006); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.4.2, 7.4.9, 7.6.2, 7.6.3
CC (Chronic HCV)	0.55	Grieve et al. (2006); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.4.2, 7.4.9, 7.6.2, 7.6.3
Recovered, no HCV, history of mild fibrosis	0.82	+0.05 added to mild fibrosis health state. Utility aligned with: Grieve et al. (2006); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011).	7.4.2, 7.4.9, 7.6.2, 7.6.3
Recovered, no HCV, history of moderate fibrosis	0.71	+0.05 added to moderate fibrosis health state.	7.4.2, 7.4.9, 7.6.2, 7.6.3
Recovered, no HCV, history of severe	0.60	+0.05 added to severe fibrosis health state. Utility aligned with: Shepherd et	7.4.2, 7.4.9, 7.6.2, 7.6.3

fibrosis (CC)		al. (2007), as referenced in Table 34 of Hartwell et al. (2011)	
DCC	0.45	Grieve et al. (2006); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.4.2, 7.4.9, 7.6.2, 7.6.3
HCC (first year)	0.45	Grieve et al. (2006); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.4.2, 7.4.9, 7.6.2, 7.6.3
HCC (subsequent year)	0.45	Grieve et al. (2006); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011)	7.4.2, 7.4.9, 7.6.2, 7.6.3
Liver transplant (first year)	0.45	Hartwell et al. (2011)	7.4.2, 7.4.9, 7.6.2, 7.6.3
Liver transplant (subsequent year)	0.67	Wright et al. (2006); Hartwell et al. (2011)	7.4.2, 7.4.9, 7.6.2, 7.6.3

CC = compensated cirrhosis; HCC = hepatocellular carcinoma; DCC = decompensated cirrhosis.
Sources:

Table 101: Summary of treatment-specific variables included in the cost-effectiveness model

Variable	Base Case Value	Source	Reference to section in submission
Treatment Duration			7.5, 7.6.1
Treatment-naive	Weeks (% Completed)*		
AbbVie Regimen	12 (98.1%-100%)	Trial publications**	
SOF + PR (GT1, GT4)	12 (97.9%)	Lawitz et al. (2013)[84]	
TPR + PR: **T12PR24** **T12PR48**	 24 (20.1%) 48 (47.7%)	Jacobson et al. (2011)[85]	
BOC + PR: **RGT- PR28** **RGT- PR48**	 28 (48.3%) 48 (22.3%)	Poordad et al. (2011)[90]	
PR (GT1)	48 (56.0%)	Jacobson et al. (2011)[85]	
PR (GT4)	48 (98.2%)	Kamal et al. (2011)[98]	
Treatment-experienced			
AbbVie Regimen	12/24 (98.1%-100.0% /94.8%)	Trial publications**	
T12PR48	48 (62.4%)	Zeuzem et al. (2011)[91]	
PR (GT1)	48 (37.9%)	Zeuzem et al. (2011)[91]	
PR (GT4)	48 (86.7%)	Poynard et al. (201)[101]	
BOC + PR: RGT	36/48 (29.3%/45.7%)	Bacon et al. (2011)[94]	
Treatment-related Health Utility*			7.4.8, 7.6.1
Treatment-naive			
AbbVie	[redacted]	Data on file[108]	

Regimen, GT1a mild		
AbbVie Regimen, GT1a moderate	[redacted]	Data on file[108]
AbbVie Regimen, GT1a cirrhosis	[redacted]	Data on file[108]
AbbVie Regimen, GT1b mild	[redacted]	Data on file[108]
AbbVie Regimen, GT1b moderate	[redacted]	Data on file[108]
AbbVie Regimen, GT1b cirrhosis	[redacted]	Data on file[108]
AbbVie Regimen, GT4 mild	[redacted]	Data on file[108]
AbbVie Regimen, GT4 moderate	[redacted]	Data on file[108]
SOF + PR (GT1, GT4)	-0.145	Younossi et al. (2013), and notes from the May 14 2014 ERG Gilead presentation[109]
TPR + PR	-0.102	TA252, Manufacturer's submission to NICE[110]
BOC + PR	-0.110^	TA253, Manufacturer's submission to NICE[111]
PR, GT1 and GT4	-0.109	TA252, Manufacturer's submission to NICE[110]
Treatment-experienced		
AbbVie Regimen, GT1a mild	[redacted]	Data on file[108]
AbbVie Regimen, GT1a moderate	[redacted]	Data on file[108]
AbbVie Regimen, GT1a cirrhosis	[redacted]	Data on file[108]
AbbVie Regimen, GT1b mild	[redacted]	Data on file[108]
AbbVie Regimen, GT1b moderate	[redacted]	Data on file[108]
AbbVie Regimen, GT1b	[redacted]	Data on file[108]

cirrhosis			
TPR + PR, GT1	-0.154	TA252, Manufacturer's submission to NICE[110]	
PR, GT1 and GT4	-0.126	TA252 Manufacturer's submission to NICE[110]	
BOC + PR, GT1	0.110^	TA253 Manufacturer's submission to NICE[111]	
Costs			
On-treatment monitoring for response and AE			7.5, 7.6.2
12 weeks AbbVie Regimen	£468.03	Based on Shepherd et al 2006/2007[57] microcosting, but inflated to 2013/14 values using PSSRU inflation indices reported in Curtis et al 2013[112]	
24 weeks of AbbVie Regimen	£936.06	Based on Shepherd et al., 2006/2007[57]	
12 weeks of SOF + PR	£468.03	Based on Shepherd et al 2006/2007	
24 weeks of therapy (TPR or BOC, + PR)	£915.87	Based on Shepherd et al., 2006/2007	
28 weeks of therapy (TPR or BOC, + PR)	£991.77	Based on Shepherd et al., 2006/2007	
36 weeks of therapy (TPR or BOC, +PR)	£1,147.66	Based on Shepherd et al., 2006/2007	
48 weeks of therapy (TPR or BOC, + PR)	£1,384.54	Based on Shepherd et al., 2006/2007	
Regimen cost per day			
AbbVie Regimen (GT1)	£416.67	AbbVie data on file	
AbbVie Regimen (GT4)	£383.34	AbbVie data on file	
SOF	£416.43	MIMS 2014	
TPR	£266.64	MIMS 2014	
BOC	£100.00	MIMS 2014	
Peg-IFN	£19.84	MIMS 2014	
RBV	£10.58	MIMS 2014	

BOC = boceprevir; GT = genotype; P = peg-IFN and ribavirin; RGT = response-guided therapy; SOF = sofosbuvir; TPR = telaprevir;
*Refers to unannualised changes in health utilities between baseline and end-of-treatment.
^A relative decrement of treatment-related utilities of 12.20% was applied to reflect the additional disutility anaemia produced on the HRQL of patients treated with BOC + PR.
Sources:
Data on file: AbbVie internal data from trials.[108]
**AbbVie trial publications (for references see Section 6 of the submission)

7.3.7 **Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.**

As mentioned previously in section 7.2, the outcome of a successful treatment is SVR observed within clinical trials for all respective regimens. Consistent with previous chronic HCV economic models, including Shepherd et al., (2007) and Hartwell et al. (2011), SVR rates per se are not extrapolated over time. However, to estimate the impact of SVR (virologic cure) on health outcomes of patients over the life time, namely on life-expectancy, quality adjusted life-years and life-time costs associated with progressive liver disease, we use an appropriate model of the natural history of chronic hepatitis C described previously.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumptions in the de novo economic model are presented in the table below.

Assumption	Justification
Patients were segmented by fibrosis stage at baseline, into mild, moderate and compensated cirrhosis. SVR was conditioned on this segmentation.	Hartwell et al. (2011) and Shepherd et al. (2007) had the same approach.
Outcomes were also conditioned on GT1a/1b status.	In order to maximise treatment outcomes of patients treated with AbbVie's regimen, sub-genotyping has to be performed. This will ensure that patients are matched to appropriate combinations of DAAs indicated to treat either GT1a or GT1b. Data from comparator regimen trials also show disparity in the rates of response (SVR) in GT1a and GT1b infected patients, thus supporting this stratification.
Hazard rates underlying transitional probabilities are constant.	Hartwell et al. (2011) and Shepherd et al. (2007) made the same assumption.
We assume that individuals are not immune from being re-infected. Reinfection after achieving SVR is represented by a small, but constant risk irrespective of the stage of liver fibrosis if individuals continue to expose themselves to risk of re-infection. Reinfection may occur at a rate of less than or equal to 1%	Expert opinion.
Patients with an SVR and a history of compensated cirrhosis have an excess risk of HCC. Mild and moderate patients have the same risk of developing HCC as the general population.	Consistent with Cardoso et al. (2010). Hartwell et al. (2011) and Shepherd et al. (2007) also made the same assumption.
Aside from risk of reinfection and excess risk of HCC for patients with an SVR and a history of compensated cirrhosis, SVR is assumed to be a permanent condition with no spontaneous reactivation of disease.	This is widely accepted concept; Koh et al., 2013. Hartwell et al., 2011 and Shepherd et al., 2007 all made a similar assumption.
Spontaneous remission is not included in the model.	Only patients who develop chronic hepatitis C absent spontaneous remission of a disease enter the Markov model.
The UK Mild HCV Trial is a source for health state utilities in the model, including for SVR states.	This trial and the associated observational studies were deemed the best source for the health state utilities for the UK chronic HCV population.
Discontinuation is based on the trials.	Expert opinion and no real world data are available for a valid comparison of discontinuation across products.
The multiple sequelae related to decompensated cirrhosis (i.e., ascites, variceal haemorrhage, hepatic encephalopathy) were combined into a single state.	Sub-manifestations of DCC are not mutually exclusive and an attempt to split out DCC into those sub-health states presents a challenge for the Markov model where a patient can only occupy one health state at a

Assumption	Justification
	time. Hartwell et al. (2011) and Shepherd et al. (2007) made the same assumption.
Patients in DCC and HCC are assumed to be candidates for liver transplantation	TP of HCC to liver transplant based on expert opinion; this transition was included in Liu et al. (2012), Hartwell et al. (2011) and Shepherd et al. (2007) all made the same assumption with regards to this transition.
All treatment effects occur in the first model cycle.	The longest therapy duration is 48 weeks.
Patients on treatment are assumed to experience a decrement in HRQL as a result of treatment adverse effects. Treatment disutilities are applied additively to baseline health state health utilities. Treatment-related disutility is annualised, and assumed to end at the end of treatment.	Hartwell et al. (2011) and Wright et al. (2006) made the same assumption.
Patients who achieve SVR experience an improvement over baseline HRQL	Wright et al. (2006) also made this assumption.
Background mortality is assumed to be the same as for the general population.	Hartwell et al. (2011) and Shepherd et al. (2007) made the same assumption.
No diagnostic costs	Patients entering the model in cycle 1 at the point when a treatment decision is being made, and hence they have already been diagnosed with HCV infection
No sub-genotyping costs	At the point of diagnosis, patients will have HCV genotype/sub-genotype tested and confirmed.
On-treatment monitoring costs are dependent on length of treatment duration, at fixed time points (e.g. week 4, 8, 12, 24, 28, 36, 48).	Expert opinion based on UK practice patterns.
Trial-based expected treatment duration is assumed, allowing for drop-outs.	Compared to assuming no drop-outs, allowing trial-based drop-outs is more realistic and conservative. One could argue that it reflects to some extent real-world adherence. We relax this assumption in scenario analysis.
Treatment duration is computed separately for each component of a given therapy	This is a more realistic and conservative way to measure the length of treatment duration (and eventually therapy cost), as it breaks treatment duration down into its components.
Discontinuation of therapy occurs at the midpoint of a reporting period (for example, in the telaprevir + PR regimen, discontinuation in the first 12 weeks is assumed to occur at week 6).	When data is not available, assume that discontinuation takes place at the midpoint of a reporting cycle, assuming a uniform distribution of discontinuation over time, which we feel is a reasonable assumption in the absence of data.
Assume AEs that are not reported for a given therapy do not occur, except in sensitivity analysis.	Trials vary in their threshold for AE reporting across publications, our assumption of zero AE for those not reported is conservative.
Assume that AEs are regimen and duration specific, but independent of fibrosis severity and genotype.	Across trials, AEs are tabulated across genotypes (e.g. NEUTRINO) and/or fibrosis severity (e.g., ADVANCE). In the model, AEs in GT4 treatment-naïve patients treated with PR are extrapolated from GT1 naïve patients treated with PR for 48 weeks.

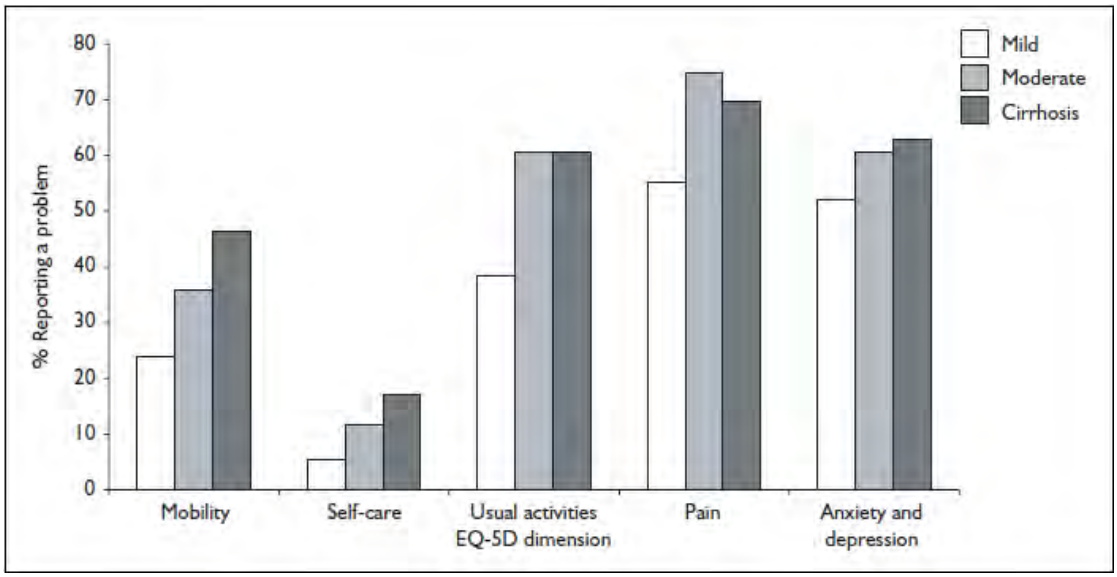
7.4 *Measurement and valuation of health effects*

Patient experience

7.4.1 **Please outline the aspects of the condition that most affect patients' quality of life.**

The effect of HCV on patient quality of life in chronically infected patients has been the subject of many studies. Chronic HCV leads to an array of symptoms that directly compromise HRQoL. Literature suggests that a degree of liver inflammation and fibrosis as a result of a direct effect of virus are amongst the most important factors negatively impacting patient's quality of life. Wright et al., 2006 found that disease symptoms tend to correlate with the degree of liver fibrosis, with the greatest proportion of patients with cirrhosis reporting severe problems in performing their usual activities compared with 3% of patients with moderate disease and 2% of patients with mild disease.[70] The figure below shows the proportion of cases in each stage of liver fibrosis reporting problems for each dimension of the EQ5D.

Figure 24: Proportion of patients with chronic HCV and different stage of liver disease reporting problems for each dimension of EQ5D from Wright et al., 2006



Hepatitis C is a systemic disease associated with many extra-hepatic manifestations in addition to hepatic inflammation and fibrosis. Symptoms like fatigue, depression and neurocognitive deficits are also found to be common in patients suffering with chronic HCV and are found to occur independent of liver disease. Another extra-hepatic manifestation found prevalent in men with chronic hepatitis C infection is sexual dysfunction. Danoff et al prospectively studied 112 men infected with HCV and reported that they were significantly more likely not to be satisfied sexually compared to HCV negative controls ($p<0.001$) and that this was associated with a significantly worse HRQoL in six out of eight domains of SF-36.[113] Danoff et al., concluded that sexual dysfunction in men is independent of depression and is associated with marked reduction in HRQoL.

Chronic HCV infection has been shown to result in lower health related quality of life (HRQoL) compared with general population. Roger et al., 1999 suggested that patients experience a decline in QoL with the diagnosis itself. In a retrospective cohort study of 34 patients, those aware of their HCV infection rated significantly worse on seven out of eight domains of the SF-36 compared with the population norm ($p<0.05$).[114] However patients unaware of their HCV status scored significantly worse only in three domains (Table 102 below).

Table 102: Mean (SD) scores in individuals aware and unaware of the HCV infection compared with mean (SE) scores in the normal population

SF-36 domain	Anti-HCV and PCR positive patients		Population norm
	Aware of serostatus (n=15)	Unaware of serostatus (n=19)	
Physical functioning	82 (17)	91 (14)	86 (0.5)
Role limitation physical	58 (45)*	75 (42)	83 (0.8)
Bodily pain	67 (26)^	82 (23)	78 (0.6)
General health	43 (27)#	64 (25)#	73 (0.5)
Vitality	49 (20)#	60 (21)#	66 (0.5)
Social functioning	65 (18)#	83 (25)	86 (0.5)
Role limitation emotional	64 (43)*	84 (30)	85 (0.8)
Mental health	66 (11)#	71 (19)^	74 (0.4)

PCR: polymerase chain reaction; SF-36: 36-item Short Form Health Survey
*$p<0.05$; ^$p<0.01$; #$p<0.001$ all compared with population norm

Stigmatisation of patients with HCV has been associated with a reduced QoL. In a cross-sectional study of 257 patients[115] diagnosed with HCV, patients completed Sickness Impact Profile and Hospital Index Depression Scale. Results showed that 57% of patients experienced stigmatisation attributable to HCV related to perceived connection of HCV with HIV/AIDS, promiscuity and substance abuse and was further associated with higher anxiety ($p<0.01$), depression ($p<0.01$) and a worsened QoL ($p<0.01$).

Therefore published evidence indicates the detrimental effect and the humanistic burden that chronic HCV exerts on patients and their QoL.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

The impact of chronic HCV on patients' HRQoL is described in the section above. In a nutshell, a patient's HRQoL is adversely impacted by the diagnosis of chronic HCV,

is likely to decrease further as chronic HCV disease progress, may decrease when on interferon-based therapies, and may increase after achieving SVR.[70]

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.

HRQoL data from Phase III clinical trials were collected by patients self-completing short form 36-version 2 (SF-36v2), a non-disease-specific HRQL instrument, followed by the EuroQoL 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L), the Hepatitis C Virus Patient Reported Outcomes Instrument (HCV-PRO) and HCV-specific function and wellbeing instrument (please refer to section 6.5 for more details). Treatment-related health utility for AbbVie's Regimen was thus estimated using EQ-5D-5L data directly collected from patients during Phase III clinical trials. The PRO instruments were completed prior to drug administration (on Day 1, i.e., baseline) and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels, based on the following schedule:

Table 103: Administration of PRO instruments during Phase III clinical trials for AbbVie's regimen

Trial name	Treatment Period						Post-Treatment Period[Ψ]				
	Baseline	Wk 4	Wk 8	Wk 12	Wk 24*	D/C**	Wk 4	Wk 12	Wk 24	Wk 36	Wk 48 or D/C**
SAPPHIRE I[#]	X	X	X	X	N/A	X	X	X	X		X
SAPPHIRE II[#]	X	X	X	X	N/A	X	X	X	X		X
PEARL I[^]	X	X	X	X	X	X	X		X		X
PEARL II	X	X	X	X	N/A	X	X	X	X		X
PEARL III	X	X	X	X	N/A	X	X	X	X	X	X
PEARL IV	X	X	X	X	N/A	X	X	X	X	X	X
TURQUOISE II	X	X	X	X	X	X	X	X	X		X

D/C: discontinuation; N/A = not applicable; Wk = week.
*Applicable only for 24-week treatment arms in TURQUOISE II and two unlicensed sub-groups of PEARL I (i.e., Groups 7-8).
**D/C: Subjects who prematurely discontinued the Treatment Period (Week 12 or Week 24 treatment arm) should have returned to the site to complete the premature D/C visit procedures. Similarly, subjects who prematurely discontinued from the Post-Treatment Period should have returned to the site to complete the Post-Treatment D/C Visit procedures.
[#]Subjects who were randomised to the placebo treatment group and completed the Open Label Treatment Period did not need to complete PRO instruments during the Post-treatment Period.
[^]EQ-5D-5L data were also collected at Week 2 - not shown in schedule above.
[Ψ] Post-treatment period data are not all currently available: TURQUOISE II data is available until post-treatment week 12.

EQ-5D in the AbbVie Regimen trials

As previously mentioned, EQ-5D-5L data were collected during AbbVie's Phase III clinical trials (with the exception of PEARL I, which is a phase II trial). Although a descriptive system for the EQ-5D-5L has been launched, studies that directly elicit

preferences from general population samples to derive value sets (tariffs) are currently under development. Therefore as no EQ-5D-5L tariff to derive utilities currently exists, a validated mapping function converting EQ-5D-5L scores to EQ-5D-3L scores known as the UK crosswalk is used within our model base-case to estimate 3D/2D treatment related utility values.[116] For EQ-5D-5L index and VAS scores, no imputation was performed for missing items.

The table below shows the estimated baseline EQ-5D-3L utility values derived from EQ-5D-5L values collected during AbbVie's regimen pivotal trials, using the UK crosswalk:

Table 104: Summary of baseline EQ-5D-3L results estimated using UK crosswalk from the EQ-5D-5L collected in AbbVie pivotal trials

Patient Cohort	Trial/Duration	Baseline Mean (95% CI)		
		Mild	Moderate	CC
G1a, Naïve	SAPPHIRE I /12 weeks	[redacted]	[redacted]	[redacted]
G1a, Experienced	SAPPHIRE II/12 weeks	[redacted]	[redacted]	[redacted]
G1b, Experienced	PEARL II/12 weeks	[redacted]	[redacted]	[redacted]
G1b, Naive	PEARL III/12 weeks	[redacted]	[redacted]	[redacted]
G1a, Naïve	PEARL IV/12 weeks	[redacted]	[redacted]	[redacted]
G1a, Naïve and Experienced*	TURQUOISE II/12 weeks	[redacted]	[redacted]	[redacted]
G1a, Naïve and Experienced*	TURQUOISE II/24 weeks	[redacted]	[redacted]	[redacted]
G1b, Naïve and Experienced	TURQUOISE II/12 weeks	[redacted]	[redacted]	[redacted]
G4, Naive	PEARL I/12 weeks	[redacted]	[redacted]	[redacted]
G4, Experienced	PEARL I/12 weeks	[redacted]	[redacted]	[redacted]

AbbVie Regimen = ABT-450/r–ombitasvir and dasabuvir ± R; CC = compensated cirrhosis; N/A = not applicable; R = ribavirin.
*In scenario analysis, we explore a situation where GT1a patients with cirrhosis are treated with 3D+R for 12 weeks if they satisfy the conditions: AFP < 20 ng/mL, or platelets ≥ 90 x 109/L, or albumin ≥ 35 g/L; if not, they are treated for 24 weeks. 71.9% of treatment-naïve patients qualify for 12 week treatment, while 59.2% of treatment-experienced patients qualify for 12 week treatment. We test this in scenario analysis.

The end-of-treatment EQ-5D-3L utility values derived from EQ-5D-5L values collected during AbbVie's regimen pivotal trials, using the UK crosswalk are summarised below:

Table 105: Summary of end-of-treatment EQ-5D-3L results estimated using UK crosswalk from the EQ-5D-5L collected in AbbVie pivotal trials

Patient Cohort	Trial/Duration	End of Treatment Mean (95% CI)		
		Mild	Moderate	CC
G1a, Naïve	SAPPHIRE I/12 weeks	[redacted]	[redacted]	[redacted]
G1a, Experienced	SAPPHIRE II/12 weeks	[redacted]	[redacted]	[redacted]
G1b, Experienced	PEARL II/12 weeks	[redacted]	[redacted]	[redacted]
G1b, Naive	PEARL III/12 weeks	[redacted]	[redacted]	[redacted]
G1a, Naïve	PEARL IV/12 weeks	[redacted]	[redacted]	[redacted]
G1a, Naive and Experienced*	TURQUOISE II/12 weeks	[redacted]	[redacted]	[redacted]
G1a, Naïve and Experienced*	TURQUOISE II/24 weeks	[redacted]	[redacted]	[redacted]
G1b, Naïve and Experienced	TURQUOISE II/12 weeks	[redacted]	[redacted]	[redacted]
G4, Naive	PEARL I/12 weeks	[redacted]	[redacted]	[redacted]
G4, Experienced	PEARL I/12 weeks	[redacted]	[redacted]	[redacted]

AbbVie Regimen = ABT- ombitasvir and dasabuvir ± R; CC = compensated cirrhosis; N/A = not applicable R = ribavirin.
*Regimen is used to treat all CC patients except G1a null CC patients

Mapping treatment-related health utility to health state health utility

The HRQoL data collected during AbbVie's pivotal trials enable treatment related health utilities to be calculated. Therefore for both 3D and 2D, treatment-related utilities have been calculated by comparing the baseline utilities with the end-of treatment utilities reported in Table 104 and Table 105 respectively. As mentioned in the above paragraph, both baseline and end-of treatment utility values have been collected using EQ-5D-5L instrument. For the purpose of the cost-effectiveness analysis and contrary to the way the utilities were analysed in our CSRs (as described in section 6.5), the UK crosswalk values were applied to all EQ-5D-5L scores elicited from the entire patient sample that participated across AbbVie pivotal trials, irrespective of their study location.

In other words, the UK crosswalk values were uniformly used to map the EQ-5D-5L scores of all trial participants to EQ-5D-3L utilities in order to obtain utilities associated with 3D/2D treatment, as perceived by the UK general population. Further, to allow for treatment-related health utilities to be applied onto the health state utility values, the change in health utilities from baseline to the end of treatment was calculated, adjusted to be annualised and then used to modify the corresponding chronic HCV health-state health utility in year one of the model. For example, if we assume a hypothetical 24-week therapy with a baseline health utility of 0.86 and an end of treatment health utility of 0.84, this therapy reduces patient health utility by 0.02 over half a year, which implies that patient's health utility over a course of one year would be reduced by 0.01 (0.02*0.5). This methodology is consistent with

previous economic evaluations, i.e. Wright et al., 2006[70], Hartwell et al., 2011[51] and also aligned with previous NICE HTA submissions in chronic hepatitis C.

Mapping

7.4.4 **If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.**

As described in the above section, the UK crosswalk was used to map EQ-5D-5L utilities collected in AbbVie's trials to EQ-5D-3L values. In the base case and a scenario analysis where AbbVie trial data is used, we apply the UK crosswalk– for simplicity, this will be referred to as "EQ-5D".

HRQL studies

7.4.5 **Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.**

A systematic review of the available literature was conducted with the aim of identifying HRQoL studies which provide utility values for model health states and could be directly used in the economic model. A recent systematic literature review undertaken by NICE, and reported by Hartwell et al.,[51] explored the same research question. Therefore, the current review was carried out as an update of the NICE review, with the aim to identify studies that have been published since the systematic review by Hartwell et al 2011.

Since the Hartwell 2011 study focused on literature published up until 2009, the current review searched the following databases from 1st January 2009 to 2nd April 2014:

- MEDLINE
- MEDLINE In-process
- EMBASE
- EconLIT
- NHS Economic Evaluations Database

Appendix 12 provides full details of the clinical keywords and medical subject headings used to search each database.

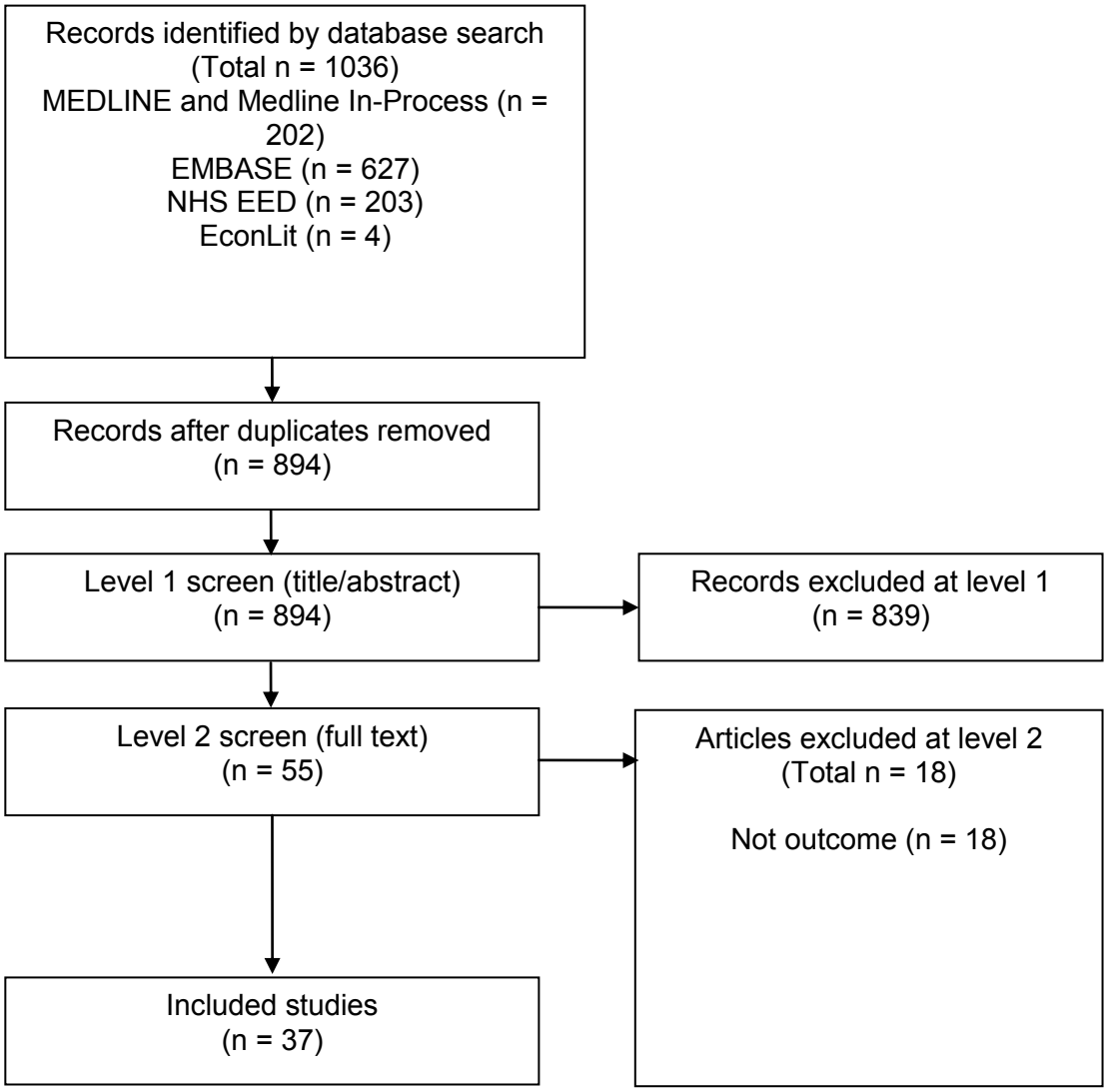
To be considered eligible for inclusion, studies had to meet pre-defined eligibility criteria developed based on the submission Scope (Table 106).

Table 106: Eligibility criteria

• Objective	• To identify studies reporting health state utility values (HSUVs) related to adult patients with chronic HCV
• Disease area	• Chronic hepatitis C
• Patient population	• Adults aged 18 years and over with chronic hepatitis C.
• Interventions and comparators	• Any intervention or comparator
• Study type	• Inclusion criteria: • Utility studies • Cost-utility analyses (CUAs) • Cost-effectiveness analyses (CEAs) • Cost-benefit analyses (CBAs) • Randomized controlled trials (RCTs) reporting HSUVs • Systematic reviews of HSUVs • Reimbursement submissions •
• Outcomes/information sought	• Studies will be included if they report a utility value related to chronic HCV, independent of treatment, using: • Generic preference based health related quality of life (HRQoL) tool (i.e. EQ-5D etc) • Non-preference based, condition specific measure which has been mapped to a preference based measure • Direct valuation of health states i.e. time-trade off, standard gamble etc •
• Literature databases	• The following databases will be searched: • MEDLINE • MEDLINE In-process • EMBASE • EconLIT • NHS Economic Evaluations Database
• Language	• English only
• Search dates	• From 2009 to present

The results of the search were exported to EndNote software and duplicates were removed. Titles and abstracts were reviewed according to the inclusion/exclusion criteria outlined in Table 106. Studies that did not meet inclusion criteria were rejected. Studies that appeared to meet inclusion criteria or that could not be excluded based on title and abstract alone were ordered for full text review. Figure 22 illustrates the study selection process using a PRISMA flow diagram.

Figure 25: PRISMA flow diagram of systematic review of HSUV studies



A total of 1,036 studies were identified from the search, of which 37 were included and underwent data extraction.

7.4.6 Provide details of the studies in which HRQL is measured.

Details of all studies are reported in Table 108. Of the 37 included studies, only 6 reported utility data published after the Hartwell 2011[51] study (please refer to Table 107). The remaining 31 sourced utility values from other sources all of which were published prior to 2009 and therefore would have been reviewed by Hartwell 2011.

Table 107: Reasons for not using in economic model

Author	Year	Reason
Crawford	2012	• Patient population reflective of chronic HCV in Asia
Fonseca	2009	• Patient population reflective of chronic HCV in Brazil • Study does not report enough information regarding the utility values

		i.e. sample size, method of valuation etc.
Cure	2014	• Treatment related utilities were estimated by taking the relative decrements of utility between baseline and SVR, sourced from the ADVANCE trial • The economic model implements the same method using the utilities on treatment observed in the Abbvie 3D clinical trial. This is preferred over the ADVANCE trial as there is more information available
Cure	2014	• Treatment related utilities were estimated by taking the relative decrements of utility between baseline and SVR, sourced from the REALIZE trial • The economic model implements the same method using the utilities on treatment observed in the Abbvie 3D clinical trial. This is preferred over the REALIZE trial as there is more information available
Hsu	2012	• Patient population reflective of chronic HCV in Canada • Method of elicitation includes mapping SF-36 to SF-6D – mapped values are not as precise as those values obtained directly from Multi Attribute Utility instruments • Study reports HUI2 and HUI3 results which are based on preferences of the US general population – NICE prefer EQ-5D to HUI2 and HUI3 • Study also reports TTO values however these do not reflect the preferences of the UK national health care service payers (UK population)
John-Baptiste	2009	• Patient population reflective of chronic HCV in Canada • Study only reports utility values for 2 groups: sustained response to antiviral therapy for chronic HCV infection and treatment failures • Study reports HUI2 and HUI3 results which are based on preferences of the US general population – NICE prefer EQ-5D to HUI2 and HUI3 • Study also reports TTO values however these do not reflect the preferences of the UK national health care service payers (UK population)
Kerr	2012	• Study only reports utility values for 2 health states related to patients with chronic HCV, with and without flu-like systems
Schafer	2009	• Sample population were all on opioid treatment – utility values reported in this study may therefore be confounded by the side effects of this drug

Table 108: Summary of included HSUV studies

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
Barros	2013	CEA	CEA – Brazil	NR – utilities sourced from published literature: Sullivan 2003 Tsukama 1993 Younossi 1999	NR	bPeg-IFN alfa – 2a plus RBV Peg-IFN alfa – 2b plus RBV	NR	NR	NR	NR	1) SVR 2) CHC 3) CC 4) DCC 5) HCC 6) LT 1st year 7) LT 2nd year	1) 0.90 2) 0.82 3) 0.78 4) 0.65 5) 0.25 6) 0.5 7) 0.7
Bjornsson	2009	Utility study	Sweden	Patients with active or previous HCV Age≥18 years	Patients recruited from 16 departments (gastetronterology/	Study reports some patients recruited in the study	472	EQ-5D	TTO	NR	1) Healthy controls 2) CHC	1) 0.819 2) 0.811

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Without liver transplant or life threatening medical problems including HCC	hepatolopgy and infectious disease) in 9 centres: 6 university hospitals and 3 community hospitals	were treated with IFN monotherapy or in combination with RBV					3) CC 4) DCC 5) SVR	3) 0.749 4) 0.656 5) 0.792
Camma	2013	CEA	CEA – Italy	NR – utilities sourced from published literature: Sullivan 2004	NR	Peg-IFN alfa and RBV Peg-IFN alfa, RBV, and BOC Peg-IFN alfa, RBV and TPR	NR	HUI3	SG	NR	1) Well 2) CHC 3) CC 4) DCC 5) HCC 6) LT	1) 1 2) 0.820 3) 0.780 4) 0.650 5) 0.250 6) 0.500

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											7) LT after 1st year	7) 0.700
Camma	2012	CEA	CEA – Italy HSUV – NR	NR – utilities sourced from published literature: Sullivan 2004	NR	Peg-IFN alfa and RBV Peg-IFN alfa, RBV, and BOC Peg-IFN alfa, RBV and TPR	NR	HUI3	SG	NR	1) Well 2) CHC 3) CC 4) DCC 5) HCC 6) LT 7) LT after 1st year	1) 1 2) 0.820 3) 0.780 4) 0.650 5) 0.250 6) 0.500 7) 0.700
Canavan	2013	CEA	CEA – UK	NR – utilities sourced from published literature:	NR	7 mutually exclusive surveillance and screening strategies	NR	EQ-5D	TTO	NR	1) Biopsy (disutility)	1) -0.05

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
			HSUV – NR	Liu 2011 Poordad 2011 Bacon 2011 Wells 2004 Grishchenko 2009 Connock 2010 Thompson 2007 Argeudas 2012							2) CHC 3) Metavir 1 4) Metavir 2 5) Metavir 3 6) CC 7) DCC 8) HCC with CC 9) HCC with DCC 10) HCC without CC 11) Palliative care 12) Following successful ablation or resection	2) 0.92 3) 0.92 4) 0.89 5) 0.89 6) 0.85 7) 0.74 8) 0.28 9) 0.3 10) 0.44 11) 0.28 12) 0.7

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											13) Recurrent HCC 14)Transplant recipient	13) 0.3 14) 0.73
Chhatwal	2013	CEA	CEA – USA HSUV – USA	NR – utilities sourced from published literature: Siebert 2003 Non-US population as study reports adjusting for US population norm	NR	Peg-IFN - RBV Peg-IFN RBV-BOC BOC response-guided therapy	NR	EQ-5D	TTO	NR	1) Drug-therapy related multiplier 2) Anaemia 3) F0, F1 4) F2, F3 5) CC 6) DCC	1) 0.90 2) 0.83 3) 0.93 4) 0.93 5) 0.90 6) 0.80

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											7) HCC 8) LT 1st year 9) Post-SVR	7) 0.79 8) 0.84 9) 1
Coffin	2012	CEA	CEA – USA HSUV – NR	NR – utilities sourced from published literature: Thein 2005 McLernon 2008	NR	US national clinical guidelines: testing HCV in patients with risk factors (i.e. drug users) Risk factor screening plus one-time screening of all US population between ages of 20-69yrs	NR	SF-36 (Original source transformed utilities to a preference-based weight)	NR	Mapping was performed Details of mapping NR	1) CHC 2) Relative added utility of no to moderate fibrosis 3) SVR	1) 0.79 2) 0.3 3) 0.86

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Nelson 2010 Ratcliffe 2002 Bownik 2010 Thompson 2008 Singer 2001 Chong 2003							4) CC 5) DCC 6) HCC 7) LT year 1 8) LT subsequent years 9) Reduced Utility: Not knowing diagnosis 10) GT 1 11) Gt 2/3	4) 0.76 5) 0.69 6) 0.67 7) 0.50 8) 0.77 9) -0.02 10) -0.07 11) -0.035

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
Crawford	2012	SR	HSUV – Asia	Patients with CHC	SR conducted to find published articles on the burden of CHC in Asia (China, India, South Korea, Taiwan and Thailand)	IFN	1,037 (combined sample size)	SF-36 mapped to:	SG (SF-6D)	Published mapping models were used to transform SF-36 data to EQ-5D and SF-6D	Utility scores for CHC patients (by study):	Utility scores (EQ-5D, SF 6D)
		HSUV			Information on recruitment of patients from individual studies NR	IFN + health intervention		EQ-5D (Ara and Brazier 2008)	TTO (EQ-5D)		1) Zhang 2007	1) 0.574, 0.623
		Synthesis				IFN + RBV		SF-6D (Ara and Brazier 2009)			2) Jin and Yao 2003	2) 0.816, 0.761
		Number of studies – 7				Peg-IFN + RBV					3) Guo 2004	3) 0.759, 0.699
											4) Wang 2005	4) 0.752, 0.711

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											5) Kang 2005 6) Chang 2008 7) Park 2003	5) 0.723, 0.726 6) 0.706, 0.684 7) 0.783, 0.726
Cure	2014	CEA	UK	Patients with CHC, genotype 1	Utilities for mild and moderate fibrosis and CC were taken from the ADVANCE clinical trial for TPR For advanced disease stages, utility data was taken from Hartwell 2009	Without treatment PR alone TVR + PR BOC + PR	NR	EQ-5D	TTO	NR	Treatment Util. from ADVANCE; other from Hartwell 2011 Mild fibrosis: 1) Without treatment 2) PR alone	1) 0.77 2) 0.675 3) 0.682 4) 0.682

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											3) TVR + PR 4) BOC + PR 5) SVR following treatment Moderate fibrosis 6) Without treatment 7) PR alone 8) TVR + PR 9) BOC + PR 10) SVR following treatment CC 11) Without treatment 12) PR alone 13) TVR + PR 14) BOC + PR	5) 0.82 6) 0.66 7) 0.579 8) 0.585 9) 0.585 10) 0.72 11) 0.55 12) 0.482 13) 0.487 14) 0.487 15) 0.61 16) 0.45 17) 0.45 18) 0.45 19) 0.67

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											15) SVR following treatment 16) DCC 17) HCC 18) LT 19) Post-LT	
Cure	2014	CEA	CEA –UK HSUV for mild and moderate fibrosis and CC – International (North America, South America, Europe, Israel and Australia)	Treatment experienced Patients with CHC, genotype 1	Utilities for mild and moderate fibrosis and CC were taken from the REALIZE clinical trial for TPR For advanced disease stages, utility data was taken from Hartwell 2009	Without treatment PR alone	NR	EQ-5D	TTO	NR	Treatment Util. from REALIZE ; other from Hartwell 2011 Mild fibrosis:	1) 0.77 2) 0.64

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
			HSUV for advanced stages - UK			TVR + PR or BOC + PR					1) Without treatment	3) 0.62
											2) PR alone	4) 0.82
											3) TVR + PR or BOC + PR	5) 0.66
											4) SVR following treatment	6) 0.53
											Moderate fibrosis	7) 0.51
											5) Without treatment	8) 0.72
											6) PR alone	9) 0.55
											7) TVR + PR or BOC + PR	10) 0.42
											8) SVR following treatment	11) 0.40
											CC	12) 0.61

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											9) Without treatment 10) PR alone 11) TVR + PR or BOC + PR 12) SVR following treatment 13) DCC 14) HCC 15) LT 16) Post-LT	13) 0.45 14) 0.45 15) 0.45 16) 0.67
Davidson	2011	CEA	CEA – Sweden HSUV Sweden	NR – utilities sourced from published literature: Foeberg 1995	NR	Diagnostic testing for HBV, HCV and HIV: Serologic tests	NR	EQ-5D	TTO	NR	Utility decrement applied to Swedish general population utility value 1) HCV	1) 0.15 (Utility decremen

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Patients with HCV based on Swedish population		Individual donors nucleic acid testing + serologic tests						t)
Deuffic-Burban	2009	CEA	CEA – France HSUV - NR	NR – utilities sourced from published literature: Thein 2005	NR	Compared 4 follow-up strategies after exposure to HCV in health care workers Patients diagnosed with HCV were all treated with peg-IFN	NR	Utility value of waiting to be informed of HCV diagnosis derived from: SF-36 (Original source transformed utilities to a preference-based weight)	NR	Yes – details of mapping NR	1) Health care workers waiting to be informed of HCV diagnosis 2) Monthly increase in utility whilst waiting for HCV diagnosis (max wait = 3 months)	1) 0.86 2) 0.04

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											3) HCV	3) 0.77
											4) No-HCV	4) 1
								Monthly increase in utility value whilst waiting for diagnosis and the HCV utility value were based on an assumption			5) HCV with peg-IFN (first 2 months)	5) 0.82
											6) HCV with peg-IFN (subsequent 2 months)	6) 0.81

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											7) HCV with peg-IFN (last 2 months) 8) HCV end of treatment response 9) SVR	7) 0.79 8) 0.80 9) 0.87
Elbasha	2013	CEA	CEA – Portugal HSUV - NR	Utilities sourced from: Wilson 2007 – patients with anaemia Chong 2003 – Canadian patients at various stages of HCV progression	NR	BOC + PR PR alone	Chong 2003 – n=193	NR	EQ-5D	NR	1) Drug therapy related multiplier 2) Anaemia multiplier 3) F0-F3	1) 0.85 2) 0.83 3) 0.76

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Wright 2006 – patients with HCV with dual therapy or no therapy							4) Compensated CC 5) DCC and post DCC 6) HCC and post HCC 7) LT 1st year 8) Post SVR	4) 0.74 5) 0.66 6) 0.65 7) 0.69 8) 0.83
Ferrante	2013	CEA	CEA – USA HSUV – NR	Patients with CHC Utilities adjusted for age by US norm Sourced from: Chong 2003	NR	Peg-IFN alfa-b + RBV+BOC Peg-IFN alfa-b + RBV	NR	NR	NR	NR	1) AV therapy no anaemia 2) AV therapy, anaemia 3) SVR, F0-F1 4) F0, F1	1) 0.90 2) 0.83 3) 1 4) 0.93

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Wilson 2007 Siebert 2003 Hanmer 2006							5) F2 6) F3 7) F4 8) DCC 9) HCC 10)LT 11) Post-LT	5) 0.93 6) 0.93 7) 0.90 8) 0.80 9) 0.79 10) 0.84 11) 0.84
Fonseca	2009	CEA	CEA – Brazil HSUV – Brazil	Patients with HCV	Panel of hepatologisits familiar with the disease and treatment	Peg-IFN +RBV IFN+RBV	NR	NR	NR	NR	1) Remission 2) Mild CHC 3) Moderate CHC 4) CC 5) Ascytis 6) Refractory ascytis 7) Heamorrhagic varices	1) 1 2) 0.98 3) 0.92 4) 0.82 5) 0.75 6) 0.52 7) 0.55

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											8) Hepatic encephalopathy 9) Hepatocarcinoma 10) Hepatic transplantation 11) Subsequent hepatic transplantation	8) 0.53 9) 0.55 10) 0.5 11) 0.7
Gellad	2012	CEA	CEA- USA	NR Utility weights sourced from published sources: Chong 2003 Sherman 2004 Thein 2005	NR	Standard duration therapy with IFN +RBV Response guided therapy with IFN + RBV	NR	NR	NR	NR	1) First year after treatment 2) SVR in subsequent 3) Mild CHC 4) Moderate CHC 5) CC	1) 0.86 2) 0.86 3) 0.79 4) 0.79 5) 0.80

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Younoussi 2001							6) Diuretic-sensitive ascites	6) 0.80
											7) Refractory ascites	7) 0.60
											8) Variceal haemorrhage (year 1)	8) 0.60
											9) Variceal haemorrhage (> 1 y)	9) 0.60
											10) Hepatic encephalopathy (year 1)	10) 0.60
											11) Hepatic encephalopathy (> 1 y)	11) 0.60
											12) HCC	12) 0.72
											13) LT y1	13) 0.73

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											14) LT (> 1y) Utilities for patients on treatment were multiplied by 0.9 to account for the disutility associated with treatment (sourced from Siebert 2009)	14) 0.73
Grieve	2009	Utility study	UK	Utilities sourced from Wright 2006	NR	Anti-viral treatment	Mild HCV (no treatment): n = 172 Mild HCV (antiviral treatment): n = 71	SF-6D EQ-5D	SG TTO	NR	1) Mild HCV (no treatment 2) Mild HCV (antiviral treatment)	SF-6D: 1) 0.724

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
							SVR: n = 20 Moderate HCV: n = 63 CC: n = 37				3) SVR 4) Moderate HCV 5) CC	2) 0.657 3) 0.787 4) 0.653 5) 0.636 EQ-5D: 1) 0.770 2) 0.654 3) 0.804 4) 0.660 5) 0.554
Grishchenko	2009	CEA	CEA – UK HSUV – NR	NR – utilities sourced from published literature: Grieve 2006	NR	Peg-IFN + RBV + antiviral treatment No treatment	NR	EQ-5D	TTO	NR	1) Mild HCV (no treatment) 2) Mild HCV (during treatment)	1) 0.77 2) 0.66

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Longworth 2003							3) SVR following treatment for mild HCV	3) 0.82
											4) Moderate HCV (no treatment)	4) 0.66
											5) Moderate HCV (during treatment)	5) 0.55
											6) SVR following treatment for moderate HCV	6) 0.71
											7) CC (no treatment)	7) 0.55
											8) CC (during treatment)	8) 0.44

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											9) SVR following treatment for CC 10) DCC 11) HCC	9) 0.60 10) 0.45 11) 0.45
Hartwell	2011	CEA	CEA – UK HUSV – UK	Utilities sourced from published literature: Shepherd 2007 Patients with CHC	Patients recruited from UK clinical trial	Peg-IFN alfa and RBV Peg-IFN alfa only	NR	EQ-5D	TTO	NR	1) SVR (from mild disease) 2) SVR (from moderate disease) 3) Mild HCV 4) Treatment for mild HCV 5) Moderate HCV 6) Treatment for moderate HCV	1) 0.82 2) 0.72 3) 0.77 4) 0.66 5) 0.66 6) 0.55

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											7) CC 8) DCC 9) HCC 10) LT 11) Post LT	7) 0.55 8) 0.45 9) 0.45 10) 0.45 11) 0.67
Hartwell	2012	CEA	CEA – UK HUSV – UK Sourced from Wright 2006	Patients with CHC	Patients recruited from UK clinical trial	shortened course of Peg-IFN combination therapy standard duration of Peg-IFN combination therapy	NR	EQ-5D	TTO	NR	1) SVR (from mild disease) 2) SVR (from moderate disease) 3) Mild HCV 4) Treatment for mild HCV 5) Moderate HCV 6) Treatment for moderate HCV	1) 0.82 2) 0.72 3) 0.77 4) 0.66 5) 0.66 6) 0.55

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											7) CC 8) DCC 9) HCC 10) LT 11) Post LT	7) 0.55 8) 0.45 9) 0.45 10) 0.45 11) 0.67

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
Hsu	2012	Utilities study	Canada	Patients with HCV: Chronically infected patients	Patients recruited from 6 tertiary care sites in Vancouver, British Columbia Patients recruited between 1 January 2006 and 1 July 2008 through a clinic advert, direct personal referrals and letters mailed from clinicians	Anti-viral therapy	Chronically infected patients: n=331 Individuals who achieved viral clearance: n=149	HUI2 HUI3	TTO SG	SF-36 data was collected and mapped to SF-6D using a published algorithm (Brazier 2002)	1) Chronically infected patients 2) Individuals who achieved viral clearance	TTO 1) 0.80

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				2) Individuals who achieved viral clearance 3) Patients on antiviral therapy 4) Patients with CC 5) Patients with HCV-related HCC 6) Individuals who had LT	Patients were asked to complete utility questionnaires by mail, at the clinic or over telephone		Patients on antiviral therapy: n=64 Patients with CC: n=137 Patients with HCV-related HCC: n=20 Individuals who had LT: n=50	SF-6D TTO			3) Patients on antiviral therapy 4) Patients with CC 5) Patients with HCV-related HCC 6) Individuals who had LT	2) 0.88 3) 0.81 4) 0.78 5) 0.78 6) 0.80

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Mix of genotype 1, 2, 3, 4 and 6 patients								HUI2 1) 0.73 2) 0.80 3) 0.71 4) 0.69 5) 0.72 6) 0.75 HUI3 1) 0.57 2) 0.70 3) 0.52 4) 0.51 5) 0.56 6) 0.64 SF-6D 1) 0.66

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
												2) 0.71 3) 0.62 4) 0.61 5) 0.61 6) 0.65
Javanbakht	2014	CEA	CEA – Iran HSUV – UK	NR - Utilities sourced from published literature: HSUVs sourced from Chong 2003 and a combination of Sutton 2008, Grieve 2006 and Shepherd 2007	NR	Methadone maintenance treatment No treatment	NR	EQ-5D	TTO	NR	1) CHC 2) CC 3) DCC 4) HCC 5) Post LT 1st year	1) 0.54 2) 0.46 3) 0.40 4) 0.37 5) 0.33

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											6) Post LT subsequent years	6) 0.49
John-Baptiste	2009	HSUV	Canada	Patients with HCV who underwent antiviral treatment Patients were split between treatment failures and those who had undetectable viral levels 6 months after antiviral therapy	Patients recruited between 1 January 2006 and 1 March 2008 through 5 health-care settings in Vancouver	Patients had been treated with conventional therapies such as: IFN alpha 2a (with RBV and without) IFN alpha 2b (with RBV and without)	Treatment failures: 103 Sustained responders : 133	HUI2 HUI3 SF-6D	TTO SG	NR	1) Treatment failures 2) Sustained responders	HUI3 1) 0.58 2) 0.7

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
						Peg-IFN alpha 2a (with RBV and without) Peg-IFN alpha 2b (with RBV and without)		TTO				HUI2 1) 0.74 2) 0.8 SF-6D 1) 0.65 2) 0.71 TTO 1) 0.84 2) 0.89
Kerr	2012	HSUV	UK	Patients with HCV with and without flu like symptoms	Patients recruited from The Hepatitis C Trust via:	Patients treated with Peg-IFN only or in combination	Not experiencing flu-like symptoms: n=48	EQ-5D	TTO	NR	Time of survey completion:	1) 0.43

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
					Patient panel Website Patient newsletter	with RBV	Experiencing flu like symptoms: n=24				1) experiencing flu-like symptoms 2) not experiencing flu-like symptoms	2) 0.73 3) 0.31 4) 0.52

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
					Online forms						Typical day when most likely experienced flu-like symptoms:	5) 0.63

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
					National support groups Treatment centres						3) at time of survey experiencing flu-like symptoms 4) at time of survey not experiencing flu-like symptoms 5) Time of survey completion, whole cohort	
Liu	2013	CEA	CEA – USA	40–74 year-old (base case age 50) U.S. adults who are unaware of	NR – Utilities sourced from published literature:	Screening strategies included:	NR	NR	NR	NR	1) F0, F1	1) 0.98

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
			HSUV - NR	their HCV infection status	Nyman 2007 Sullivan 2006 Salomon 2003 Grieve 2006 Sherman 2004 Chong 2003 McLernon 2008	No screening Risk-factor guided screening Birth-cohort screening.					2) SVR after F0, F1 3) F2, F3 4) SVR after F2, F3 5) F4 6) SVR after F4 7) DCC 8) HCC 9) LT	2) 1 3) 0.85 4) 0.933 5) 0.79 6) 0.933 7) 0.72 8) 0.72 9) 0.825
Liu	2012	CEA	CEA-USA HSUV – NR	NR – Utilities sourced from published literature: Salomon 2003	NR	New protease inhibitors and an Interleukin-28B (IL-28B) genotyping assay for	NR	NR	NR	NR	1) F0, F1 2) SVR after F0, F1	1) 0.98 2) 1

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Nyman 2007 Sullivan 2006 Grieve 2006 Sherman 2004 Chong 2003 McLernon 2008		treating chronic HCV					3) F2, F3 4) SVR after F2, F3 5) F4 6) SVR after F4 7) DCC 8) HCC 9) LT	3) 0.85 4) 0.933 5) 0.79 6) 0.933 7) 0.72 8) 0.72 9) 0.825
Liu	2011	CEA	CEA – USA HSUV – NR	NR – Utilities sourced from published literature: Salomon 2003 Grieve 2006 Sherman 2004	NR	FibroTest (non-invasive biomarker assay for fibrosis) Liver biopsy	NR	NR	NR	No mapping was conducted	1) F0, F1 2) SVR after F0, F1 3) F2, F3 4) SVR after F2, F3	1) 0.98 2) 1 3) 0.85 4) 0.93

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Chong 2003 McLernon 2008							5) F4 6) SVR after F4 7) DCC 8) HCC 9) LT	5) 0.79 6) 0.93 7) 0.72 8) 0.72 9) 0.81
Martin	2013	CEA	CEA – UK HSUV – UK and Scotland	NR – Utilities sourced from published literature: McDonald 2013	NR	Dried blood spot testing	NR	NR	NR	NR	1) Uninfected 2) Mild 3) Moderate 4) CC 5) DCC 6) HC 7) LT 8) Post LT	1) 0.94 2) 0.77 3) 0.66 4) 0.55 5) 0.45 6) 0.45 7) 0.45 8) 0.67

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											9) Mild – on treatment 10) Moderate - on treatment 11) CC - on treatment 12) Mild SVR 13) Moderate SVR 14) CC SVR	9) 0.66 10) 0.55 11) 0.46 12) 0.82 13) 0.72 14) 0.61
Martin	2012	CEA	CEA - UK HSUV – NR	NR – Utilities sourced from published literature: Vickerman 2008 Sutton 2008	NR	Peginterferon-alpha+ ribavirin	NR	NR	NR	NR	1) Uninfected Ex/non-IDU 2) Uninfected IDU 3) Mild HCV	1) 1 2) 0.85 3) 0.77

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Grieve 2006 Shepherd 2007 Wright 2006							4) Moderate HCV 5) CC 6) DCC 7) HCC 8) LT 9) Post LT 10) Mild – on treatment 11) Moderate - on treatment 12) Mild SVR 13) Moderate SVR	4) 0.66 5) 0.55 6) 0.45 7) 0.45 8) 0.45 9) 0.67 10) 0.66 11) 0.55 12) 0.82 13) 0.72

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
Martin	2011	CEA	CEA – UK HSUV – NR	NR – Utilities sourced from published literature: Vickerman 2008 Sutton 2008 Grieve 2006 Shepherd 2007 Wright 2006	NR	Antiviral treatment	NR	NR	NR	NR	1) Uninfected Ex-/non-IDU 2) Uninfected IDU 3) Mild HCV 4) Moderate HCV 5) CC 6) DCC 7) HCC 8) LT 9) Post LT 10) Mild – on treatment	1) 1 2) 0.85 3) 0.77 4) 0.66 5) 0.55 6) 0.45 7) 0.45 8) 0.45 9) 0.67 10) 0.66

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											11) Moderate - on treatment 12) Mild SVR 13) Moderate SVR	11) 0.55 12) 0.82 13) 0.72
McEwan	2013	CEA	CEA – UK HSUV – UK	NR – Utilities sourced from published literature: Martin 2012	NR	Response-guided treatment algorithm based on virological response and baseline viral load	NR	EQ-5D	NR	NR	1) Baseline 2) On treatment (F0,F1)	1) 0.85 2) 0.66

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											3) On treatment (F2,F3)	3) 0.55
						standard duration of therapy ((PEG-IFN-alpha-2a) + ribavirin)					4) SVR	4) 0.82
											5) Chronic HCV(F0)	5) 0.77
											6) Chronic HCV(F1)	6) 0.77
											7) Chronic HCV(F2)	7) 0.66
											8) Chronic HCV(F3)	8) 0.66
											9) Chronic HCV(F4)	9) 0.55
											10) DCC	10) 0.45

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											11) HC 12) LT 13) LT after 1st year	11) 0.45 12) 0.45 13) 0.45
McGarry	2012	CEA	CEA – USA HSUV – NR	NR – Utilities sourced from published literature: Singer 2001	NR	Birth-cohort screening program for Hepatitis C screening 100% of U.S. residents born 1946-1970 over 5 years (birth-cohort screening)	NR	NR	NR	NR	1) F0-F3 2) F4	1) 0.96 2) 0.8

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Kim 1997 Younossi 2001 Roger 1999		current risk-based screening					3) Treatment 4) Failed treatment 5) DCC 6) C 7) LT 1st year 8) LT after 1st year	3) 0.9 4) 0 5) 0.56 6) 0.25 7) 0.8 8) 0.95
Ruggeri	2013	CEA	CEA – Italy HSUV – NR	NR – Utilities sourced from published literature: Nakamura 2008 Sullivan 2004	NR	Anti-HCV screening program compared to no screening	NR	NR	NR	NR	1) HCV 2) CC 3) DCC	1) 0.82 2) 0.78 3) 0.65

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				Siebert 2003							4) HCC 5) LT 6) Combination therapy 7) Viral positive	4) 0.25 5) 0.5 6) 0.9 7) 0.98
Schafer	2009	12 month Cohort study	Germany	At least 16 years old, prevalence cohort with regards to agonist maintenance therapy for opioid dependence with either buprenorphine or methadone	Patients on substitute doctors register lists in Germany were contacted	Patients receiving methadone or buprenorphine	2414	EQ-5D	NR	NR	1) HCV 2) No HCV 3) HCV with antivirals	Baseline values: 1) 0.71 2) 0.74

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											4) HCV without antivirals	3) 0.72 4) 0.71 Follow-up values: 1) 0.71 2) 0.75 3) 0.72 4) 0.71
Siebert	2009	CEA	Germany	NR – Utilities sourced from published literature: Siebert 2003	NR	No antiviral therapy IFN alfa 2b plus RBV Peg-IFN alfa 2b + weight-based RBV	NR	NR	NR	NR	1) Mild chronic hep 2) Mod chronic hep 3) CC	1) 0.95 2) 0.92 3) 0.89

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
						PegIFN-alpha-2b + RBV					4) DCC or HC 5) HC 6) LT	4) 0.81 5) 0.81 6) 0.86
Turnes	2013	CEA	CEA – Spain HSUV – NR	NR – Utilities sourced from published literature: Kim 1997	NR	Peg-IFN alfa-2a Peg-IFN alfa-2b + RBV	NR	EQ-5D	NR	NR	1) CHC 2) SVR <= 44 yrs 3) SVR <= 54 yrs 4) SVR <= 64 yrs 5) SVR <= 74 yrs 6) SVR >= 75 yrs 7) CC 8) DCC 9) HCC 10) LT 1st year	1) 0.82 2) 0.91 3) 0.84 4) 0.78 5) 0.78 6) 0.75 7) 0.78 8) 0.65 9) 0.25 10) 0.5

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
											11) LT after 1st year	11) 0.7
Younossi	2014	CEA	CEA – USA HSUV – NR	NR – Utilities sourced from published literature: Chong 2003 Sherman 2004 Younossi 2001 Liu 2011 McLernon 2008 Ratcliffe 2002	NR	All patients treated with IFN+RBV+DAA Oral therapy (combination of oral agents, all IFN-free)	NR	NR	NR	NR	1) CHC 2) CC 3) SVR 4) DCC 5) HCC 6) LT 1st year 7) LT subsequent year	1) 0.84 2) 0.82 3) 0.93 4) 0.71 5) 0.72 6) 0.67 7) 0.73

Author	Year	Study type	Country	Patient population in which health effects are measured	Patient recruitment	Intervention and Comparators	Sample size	Method of elicitation	Method of valuation	Mapping	Health States	Results
				McEwen 2013 Siddiqui 2008							8) Disutility related to IFN treatment 9) Disutility related to oral therapy	8) 0.11 9) 0.03

BOC, Boceprevir; CC, Cirrhosis; CEA, Cost-Effectiveness Analysis; CHC, Chronic Hepatitis C; DAA, Direct Acting Anti-viral Agents; DCC, Decompensated Cirrhosis; EQ-5D, European Quality of Life-5 Dimensions; F0, Fibrosis stage 0; F1, Fibrosis stage 1; F2, Fibrosis stage 2; F3, Fibrosis stage 3; F4, Fibrosis stage 4; GT, Genotype; HBV, Hepatitis B Virus; HCC, Hepatocellular Carcinoma; HIV, Human Immuno-deficiency Virus; HSUV, Health State Utility Values; HUI2, Health Utilities Index 2; HUI3, Health Utilities Index 3; IDU, Injection Drug Users; IFN, Interferon; LT, Liver Transplant; NR, Not reported; Peg-IFN, Pegylated Interferon; RBV, Ribavirin; SF-36, Short Form 36 Health Survey; SF-6D, Short Form 6 Dimension Health Survey; SG, Standard Gamble; SVR, Sustained Virological Response; TPR, Telaprevir; TTO, Time Trade Off

In summary, the results of the systematic review focusing on 6 studies reporting utilities and published after Hartwell 2011 did not identify any utility sources deemed more appropriate than those used in the most recent UK HTA (Hartwell 2011) – the reasons for this are outlined in Table 107. As a result, health state based utilities chosen for the model base case were the same as those used in Hartwell 2011, the original sources of which are derived from Wright 2006. [70] The comparator treatment-based health utilities are based on data analysed from the available literature of comparator regimens, which include published STA submissions to NICE.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Baseline EQ-5D scores captured in 6 pivotal multi-centre Phase III trials were somewhat higher than those used in Wright et al. (2006) (see Section 7.4.9). For instance, patients with mild HCV recorded utilities that ranged between 0.79 and 0.87 in the trials, whereas the corresponding utility value was 0.77 in Wright et al. (2006). The trial utilities of patients with compensated cirrhosis ranged from 0.78 to 0.83 (AbbVie trials) compared to 0.55 (Wright, et al. (2006)). As described in section 7.4.2 for the purpose of the cost-effectiveness analysis, the EQ-5D-5L health state valuations were converted into a single preference based health utility index score by applying the UK crosswalk to all patients irrespective of their country of origin. However, as the UK patients represented only 5.7% of the total enrolled adult patient sample (133/2308), AbbVie feels that these utilities would not be representative of the UK patients suffering with chronic hepatitis C and thus decided against using them in the model base case. Instead we source the health state utilities from Wright et al 2006 and Hartwell et al., 2011, thus providing the source of the data which are consistent with those incorporated in a number of previous economic analyses. However we test this approach in a scenario analysis where we substitute base-case health state utilities for the trial baseline utilities (Table 104) for patients with the mild, moderate, compensated cirrhosis, and SVR states. Moreover, the trial HRQoL data apply only to patients with mild, moderate and compensated cirrhosis as AbbVie clinical trials only included patients with mild, moderate and compensated cirrhosis, and did not enroll patients with more severe HCV health states, e.g., DCC, HCC, that are included in the model. For health states beyond compensated cirrhosis, such as DCC and HCC, we extrapolate the decrement observed in Wright et al. (2006)[70] between mild health state and DCC and HCC onto the EQ-5D scores of mild Hep C patients collected in our trails to derive utility values for DCC and HCC.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Interferon and ribavirin combination therapy for HCV produces a number of well-documented side-effects that are dominated by fatigue, influenza like symptoms, headache, nausea, depression, irritability, sleeping disorders, skin reactions, dyspnea, haematological and biochemical abnormalities such as neutropenia, anaemia, thrombocytopenia and ALT elevations. These abnormalities are known to have negative impact on patients' HRQoL and in some cases may be treatment limiting, require dose reduction or drug discontinuation which in turn may impair treatment response. Patients treated with PR-based therapies, such as SOF + PR, TPR + PR and BOC + PR, report many of the same AEs as those treated with PR alone (see section 7.3.1). In addition, patients treated with TPR + PR experience rash and anaemia more frequently. On the other hand, patients treated with BOC + PR experience anaemia and dysgeusia with greater frequency. Competitors' on-treatment (dis)utilities are summarised in the table below:

Table 109: On-treatment (dis)utilities for competitor therapies

Treatment-naïve*		
SOF + PR (GT1, GT4)	-0.145	Younossi et al. (2013), and notes from the May 14 2014 ERG Gilead presentation[109]
TPR + PR	-0.102	TA252, Manufacturer's submission to NICE[110]
BOC + PR	-0.110^	TA253, Manufacturer's submission to NICE[111]
PR, GT1 and GT4	-0.109	TA252, Manufacturer's submission to NICE[110]
Treatment-experienced*		
TPR + PR, GT1	-0.154	TA252, Manufacturer's submission to NICE[110]
PR, GT1 and GT4	-0.126	TA252 Manufacturer's submission to NICE[110]
BOC + PR, GT1	0.110^	TA253 Manufacturer's submission to NICE[111]

*Refers to unannualised changes in health utilities between baseline and end-of-treatment.
^A relative decrement of treatment-related utilities of 12.20% was applied to reflect the additional disutility anaemia produced on the HRQL of patients treated with BOC + PR.

The majority of AEs observed in the AbbVie Regimen trials are mild or moderate. The safety analysis of the AbbVie Regimen, which is presented in Section 6.8 shows that AEs occurred at very low rates across all trials.

AbbVie's regimen on-treatment (dis)utilities are summarised in the table below:

Table 110: On-treatment (dis)utilities for AbbVie's regimen

Treatment-naïve*		
AbbVie Regimen, GT1a mild	[redacted]	Data on file[108]
AbbVie Regimen, GT1a moderate	[redacted]	Data on file[108]
AbbVie Regimen, GT1a cirrhosis (12 weeks)	[redacted]	Data on file[108]
AbbVie Regimen, GT1a cirrhosis (24 weeks)	[redacted]	Data on file[108]
AbbVie Regimen, GT1b mild	[redacted]	Data on file[108]
AbbVie Regimen, GT1b moderate	[redacted]	Data on file[108]
AbbVie Regimen, GT1b cirrhosis	[redacted]	Data on file[108]
AbbVie Regimen, GT4 mild	[redacted]	Data on file[108]
AbbVie Regimen, GT4 moderate	[redacted]	Data on file[108]
Treatment-experienced*		
AbbVie Regimen, GT1a mild	[redacted]	Data on file[108]
AbbVie Regimen, GT1a moderate	[redacted]	Data on file[108]
AbbVie Regimen, GT1a cirrhosis (12 weeks)	[redacted]	Data on file[108]

AbbVie Regimen, GT1a cirrhosis (24 weeks)	[redacted]	Data on file[108]
AbbVie Regimen, GT1b mild	[redacted]	Data on file[108]
AbbVie Regimen, GT1b moderate	[redacted]	Data on file[108]
AbbVie Regimen, GT1b cirrhosis	[redacted]	Data on file[108]

*Refers to unannualised changes in health utilities between baseline and end-of-treatment.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 **Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.**

HRQL in the model

Health utility in the model is allocated to each health state and treatment, respectively giving rise to:

1) health state utility (i.e., each health state in the model is associated with an annualised health utility); and

2) treatment-related health utility.

Health state-based health utility

Health state-based health utility reflects the expected annual health utility from chronic HCV over the complete disease course. Our base-case health state utility values are derived from the published literature, namely from Hartwell et al. (2011)[51] who in turn uses utilities reported in Wright et al. (2006)[70]. Wright et al. (2006) showed that as disease progress from mild fibrosis to compensated cirrhosis, health utility (based on the EQ-5D) declines from 0.77 to 0.55. More advanced liver disease is associated with even lower utilities, e.g., 0.45 for DCC and HCC. We test these values in DSA, by varying individually the base case health state utilities. Experience of SVR, captured in the model by the “Recovered” states, has shown to positively improve baseline HRQoL. Based on Wright et al. (2006), SVR from mild fibrosis, moderate fibrosis or compensated cirrhosis is associated with a 0.05 increase in health utility. We test this assumption on improvement in a scenario analysis. Increase in health utility due to successful treatment is assumed to occur in the second model cycle for those who experience SVRs.

Treatment-related health utility

Treatment-related health utility reflects the effect of treatment on HRQL; its duration is assumed to be limited and to correspond to the time a patient is on therapy. For all treatments, including the AbbVie’s Regimen treatment-related health utility reflects a decrement over the duration of each respective therapy (e.g., 12, 24 or 48 weeks).

Prior to the AbbVie Regimen, most HCV combination therapies involved peg-IFN and potentially long, complex dosing; To date, these therapies have been associated with

“disutility” or reduction in health utility, for patients on therapy, owing to the AE profile and poor tolerability of these regimens.

Treatment-related health utility was derived from the EQ-5D-5L PRO instruments in the SAPPHIRE, PEARL and TURQOUISE trials for the AbbVie’s Regimen, and from the published literature for the comparator regimens.

Treatment-related health utility: data analysis and calculation

Using HRQL data from published trials, we compute the utility decrement associated with treatment with PR, SOF + PR, TPR + PR, BOC + PR, and the AbbVie Regimen in GT1 as well as GT4 patients. This is achieved by taking the difference between the baseline and end-of-treatment HRQLs from each trial. Table 111 below summarises the results.

Table 111: Summary of treatment-related health decrements applied in the model (presented unannualised)

GT/ SubGT	Treatment	Fibrosis Severity	Treatment-naïve	Treatment-experienced	Reference
1a	AbbVie Regimen	Mild Moderate CC (12 week) CC (24 week)	[redacted]	[redacted]	Data on file
1b	AbbVie Regimen	Mild Moderate CC	[redacted]	[redacted]	Data on file
4	AbbVie Regimen	Mild Moderate	[redacted]	[redacted]	Data on file
1, 4	SOF + PR	All	-0.145	N/A	Younossi et al. (2013); notes from the May 14 2014 ERG Gilead presentation.
1	TPR + PR	All	-0.102	-0.154	TA252
1	BOC + PR	All	-0.110*	-0.110*	TA253
1	PR	All	-0.109	-0.126	TA252
4	PR	All	-0.109**	-0.126**	TA252

AbbVie Regimen = ABT-450/r–ombitasvir and dasabuvir ± R; BOC= boceprevir; CC = compensated cirrhosis; GT = genotype; N/A = not applicable; PR = peg-IFN and ribavirin; R = ribavirin; SOF = sofosbuvir; subGT = sub-genotype; TPR = telaprevir. Reported to 3 decimal places.

^We combine the joint utility decrement for GT1a naïve patients by combining results from the appropriate patient segment of the SAPPHIRE I and PEARL IV studies.

^^ In a scenario analysis, GT1a patients with cirrhosis are treated with 3D+R for 12 weeks if they satisfy the conditions: AFP < 20 ng/mL, or platelets ≥ 90 x 109/L, or albumin ≥ 35 g/L; if not, they are treated for 24 weeks. In the base case, we assume all GT1a patients with cirrhosis are treated with 24 weeks.

*A relative decrement of treatment-related utilities of 12.20% was applied to reflect the additional disutility anaemia produced on the HRQL of patients treated with BOC + PR.

**In the absence of data, we assume the same utility decrement for GT4 patients treated with PR as GT1 patients in the ADVANCE (treatment-naïve) and REALIZE (treatment-experienced) PR arms respectively.

In the model, the above reported utility values are annualised by adjusting each regimen by its respective trial-based regimen duration. Thereafter, annualised disutilities are applied to baseline utilities per Wright et al. (2006), to arrive at on-treatment utilities. For example, if we assume that for a 12-week treatment regimen, baseline EQ-5D is 0.90 and end-of-treatment EQ-5D is 0.89 annualised utility decrement over the 12-week duration is: -0.01*12/52=-0.0023. Thus, for a patient with mild fibrosis, on-treatment utility is = 0.77-0.023=0.768. We account for different treatment durations of regimens in the annualised computation of disutility rates. In addition, we take into account trials in which treatment was based on a response-guided therapy e.g., T12PR arm in ADVANCE and RGT arms in SPRINT-2 and RESPOND-2. See also Section 7.5, where we describe the computation of therapy duration applied in the model. Thereafter, annualised treatment-related health utility decrements are applied to baseline health state utilities in cycle one in which treatment is received (as per Wright et al. (2006)). The results are shown in the table below.

Table 112: Annualised treatment-related health utility decrements for mild, moderate and compensated cirrhosis health states

Health state	Mild	Moderate	Compensated cirrhosis
Baseline*	0.77	0.66	0.55
On-treatment (first cycle), treatment-naïve, GT1			
AbbVie Regimen, 1a+			
12weeks	[redacted]	[redacted]	[redacted]
24weeks			
AbbVie Regimen, 1b			
SOF + PR	-0.0335	-0.0335	-0.0335
PR	-0.1006	-0.1006	-0.1006
TPR + PR	-0.0669	-0.0669	-0.0669
BOC + PR	-0.0782	-0.0782	-0.0782
On-treatment (first cycle), treatment-experienced, GT1			
AbbVie Regimen, 1a^+			
12 weeks	[redacted]	[redacted]	[redacted]
24 weeks			
AbbVie Regimen, 1b^	[redacted]	[redacted]	[redacted]
PR^	-0.1163	-0.1163	-0.1163
TPR + PR^	-0.1422	-0.1422	-0.1422
BOC + PR^	-0.0999	-0.0999	-0.0999
On-treatment (first cycle), treatment-naïve, GT4			
AbbVie Regimen	[redacted]	[redacted]	[redacted]
SOF + PR	-0.0335	-0.0335	-0.0335
PR#	-0.1006	-0.1006	-0.1006
On-treatment (first cycle), treatment-experienced, GT4			
AbbVie Regimen	[redacted]	[redacted]	[redacted]
PR^#	-0.1163	-0.1163	-0.1163

*Utilities taken from Wright et al. 2006;[70]

[+] In scenario analysis, we explore a situation where GT1a patients with cirrhosis are treated with 3D+R for 12 weeks if they satisfy the conditions: AFP < 20 ng/mL, or platelets ≥ 90 x 109/L, or albumin ≥ 35 g/L; if not, they are treated for 24 weeks.
[^]This includes null response, partial response and prior relapse patients.
[#]This is assumed to be the same as GT1 patients of PR arm in ADVANCE (treatment-naïve) and REALIZE (treatment-experienced) trials.

In general, the lower treatment-related health utility decrements experienced by patients on the AbbVie Regimen and SOF + PR reflect the shorter treatment duration of 12 weeks (except for GT1a, compensated cirrhotic patients), compared to other regimens. However, the lower treatment-related health utility decrement of the AbbVie Regimen compared to SOF + PR likely stems from its exclusion of peg-IFN, and correspondingly, the lack of side-effects arising from its use.

Summary of base case on health utilities in the model

The base case health state-based utilities are from Wright et al. (2006)[70] subsequently quoted by Shepherd et al., 2007[57], Hartwell et al. 2011[51] as well as the past and the currently ongoing NICE HTAs in chronic hepatitis C. The Recovered health states assume a + 0.05 increase in health utility. Treatment-related health utility for the comparator regimens are from published data in the base case and all sensitivities – there were no identifiable data for sensitivity analysis on these values. The treatment-related health utility for the AbbVie's Regimen is based on the annualised difference in health utility between the baseline and end of treatment. Trial-based EQ-5D-5L was mapped to EQ-5D (-3L) using the UK crosswalk. The base-case health state utilities (stratified by fibrosis severity) are also varied in DSA (± 20%). Scenario analyses explored are described in Section 7.6.1.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:

The applicability of chosen health state utilities was not assessed by clinical experts.

7.4.11 **Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?**

Previous studies have linked decrements in patient HRQL to the severity of liver disease, with the lowest utility scores seen in patients with decompensated cirrhosis or hepatocellular carcinoma (please refer to section 7.4.1). For instance Wright et al. (2006) showed that as disease progresses from mild fibrosis to compensated cirrhosis, health utility declines from 0.77 to 0.55 based on the EQ-5D.70 Advanced liver disease is further associated with even lower utilities, e.g., 0.45 for DCC and HCC. Therefore a change in patients HRQL is captured within AbbVie's model through the natural history of a disease progression and the life time horizon adopted in the model base case.

7.4.12 **Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?**

No health effects identified in the literature or clinical trials have been excluded from the analysis.

7.4.13 **If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?**

The baseline quality of life analysis for patients in the mild, moderate and compensated cirrhosis states is based on the UK Mild HCV Trial, observational study and liver transplantation study, as described previously by Wright et al. (2006); in the base case; additive changes from the trials reflecting treatment related (dis)utilities were mapped onto the baseline health state utilities as described in section 7.4.9. In a scenario analysis, we replace utilities from Wright et al., 2006 with AbbVie trial utilities for baseline and recovered health states, as described in sections 7.4.3 and 7.4.7.

7.4.14 **Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.**

HRQoL is assumed to be constant over time for as long as a patient remains within the same health state. However, as patients progress to a more severe health states over time or achieve SVR, HRQoL changes.

7.4.15 **Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.**

No values have been amended.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 **Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.**

In our submission, costs for the clinical management of chronic hepatitis C have been sourced from the published literature are made up of two main components:

a) Health state costs – are costs 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. A retrospective chart review of patients with CHC was identified in our systematic review of resource use (Backx et al., 2014[118]). This study evaluated resource use amongst HCV patients in the East Midlands region of the UK according to their response to treatment (SVR or Non-SVR). Data were captured for each separate disease state occupied by the patient (chronic hepatitis and cirrhosis). Unit costs relating to resource use items were taken from the NHS payment by results database. We thus use costs reported by Backx et al., 2014 as estimates of health state costs for SVR (recovered health states), mild and moderate fibrosis and compensated cirrhosis. In the absence of more recent or relevant sources, costs of more advanced stages of liver disease (DCC, HCC, liver transplant) were obtained from Shepherd 2007/Hartwell 2011 and updated to current values using the PSSRU pay and prices inflation index (Curtis 2013). For more information refer to section 7.5.6.

b) Treatment related costs – consist of drug acquisition costs x mean treatment duration from trials and costs associated with on-treatment monitoring for response and adverse events to treatment (excess costs of health service contacts for patients undergoing treatment). For further details, please refer to section 7.5.5.

Treatment related costs: calculating mean treatment duration from trials

The cost of therapy depends on the daily price of the components of a given regimen, multiplied by the mean duration of treatment. We describe below our approach to estimate mean treatment duration for all regimens from published trial data.

In order to obtain an accurate estimate for the actual duration of therapy, we take into account patients that drop out during trials. This method allows us to derive 'trial-based' treatment duration; it may be argued that this also captures 'real world' adherence to some degree.

We retrieve from published clinical trials the number of patients who 1) received at least one dose of the study drug, 2) completed the study, and 3) discontinued the study early. For patients who discontinued early, we determine their average duration of therapy by assuming that discontinuation occurred at the mid-point of trial duration.

Assuming that information on the average duration of therapy for those who discontinued early is not available, the average treatment duration in a given trial will be calculated as follows:

$$\begin{aligned} Average\ Treatment\ Duration \\ &= \left\{\frac{A}{A+B} \times Total\ Treatment\ Duration\right\} \\ &+ \left\{\frac{B}{A+B} \times Total\ Treatment\ Duration \times 0.5\right\} \end{aligned}$$

where,
A is the number of patients who completed study
B is the number of patients who did not complete the study

(1)

If the average treatment duration for patients who discontinued the study is known, we replace "Total Treatment Duration x 0.5" with "Average treatment duration for patients who discontinued study".

In some trials, there is more than one study group within a treatment arm of a trial, and each group has different treatment duration (e.g., T12PR treatment arm in ADVANCE, where, based on trial outcomes to week 12, some patients receive 24 weeks of PR while others receive 48 weeks of PR). In this case, the formula to obtain the average duration is weighted by the sample size of each group. For example, when there are 2 groups within a treatment arm, the previous formula becomes:

$$\begin{aligned} Average\ Treatment\ Duration \\ &= \frac{A+B}{A+B+C+D}\left\{\left[\frac{A}{A+B} \times Total\ Treatment\ DurationGroup\ 1\right]\right. \\ &\left. + \left[\frac{B}{A+B} \times Total\ Treatment\ DurationGroup\ 1 \times 0.5\right]\right\} \\ &+ \frac{C+D}{A+B+C+D}\left\{\left[\frac{C}{C+D} \times Total\ Treatment\ DurationGroup\ 2\right]\right. \\ &\left. + \left[\frac{D}{C+D} \times Total\ Treatment\ DurationGroup\ 2 \times 0.5\right]\right\} \end{aligned}$$

where ,
A is the number of patients who completed the study in Group 1
B is the number of patients who did not complete the study in Group 1
C is the number of patients who completed the study in Group 2
D is the number of patients who did not complete the study in Group 2

(2)

The table below summarises the trial duration and proportion of patients who completed treatment in each trial arm for the AbbVie Regimen as applied in the economic model.

Table 113: Trial-based treatment duration for the AbbVie Regimen

Patient Segment	GT/ SubGT	Fibrosis Stage	Trial/Duration (weeks)	% patients completing regimen
Naïve	GT1a	No cirrhosis	SAPPHIRE I/12	98.1% (464/473)
Naïve	GT1a	No cirrhosis	PEARL IV/12	100% (100/100)

Naïve	GT1a	Cirrhosis	TURQUOISE II/12	98.1% (204/208)
Naïve	GT1a	Cirrhosis	TURQUOISE II/24	94.8% (163/172)
Naïve	GT1b	No cirrhosis	PEARL III/12	99.5% (208/209)
Naïve	GT1b	Cirrhosis	TURQUOISE II/12	98.1% (204/208)
Experienced	GT1a	No cirrhosis	SAPPHIRE II/12	98.3% (292/297)
Experienced	GT1a	Cirrhosis	TURQUOISE II/12	98.1% (204/208)
Experienced	GT1a	Cirrhosis	TURQUOISE II/24	94.8% (163/172)
Experienced	GT1b	No cirrhosis	PEARL II/12	100% (95/95)
Experienced	GT1b	Cirrhosis	TURQUOISE II/12	98.1% (204/208)
Naïve	GT4	No cirrhosis	PEARL I/12	97.6% (41/42)
Experienced	GT4	No cirrhosis	PEARL I/12	100% (49/49)

AbbVie Regimen = ABT-450/r–ombitasvir and dasabuvir ± R; Cirrhosis = compensated cirrhosis, F4; Experienced = Null response, partial response, prior relapse; GT = genotype; No cirrhosis = mild/moderate fibrosis, F0-F3; R = ribavirin; SubGT = sub-genotype.
GT1a patients with cirrhosis are treated for 24 weeks in the base case. Treatment with 3D+R for 12 weeks is explored in a scenario analysis if patients satisfy the conditions: AFP < 20 ng/mL, or platelets ≥ 90 x 109/L, or albumin ≥ 35 g/L; if not, they are treated for 24 weeks.
Sources:
Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370(17):1594-603.
Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370(17):1604-14.
Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, Ritonavir, Ombitasvir, and Dasabuvir Achieves 97% and 100% Sustained Virologic Response With or Without Ribavirin in Treatment-Experienced Patients With HCV Genotype 1b Infection. Gastroenterology 2014;147(2):359-65.
Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r–ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370(21):1983-92.
Poordad F, Hezode C, Trinh R, et al. ABT-450/r–ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370(21):1973-82.
Pol S, Reddy R, Baykal T et al. Interferon-free regimens of Ombitsasvir and ABT-450/r with or without ribavirin in patients with HCV genotype 4 infection: PEARL-I study results. Hepatology. AASLD Abstracts. 2014; 60(4 Suppl): 1129A.

The table below summarises the trial duration and proportion of patients who completed treatment in each trial arm for the comparator regimens as applied in the economic model.

Table 114: **Trial-based treatment duration for comparators in the model**

Regimen	Treatment experience	Regimen Duration (weeks)	% patients completing regimen	Source
SOF + PR	Naïve (GT1, GT4)	12	97.9% (320/327)	Figure S1, Lawitz et al. (2013)
T12PR24*	Naïve	24	20.1% (195/363)	Figure 1, Jacobson et al. (2011)
T12PR48*	Naïve	48	47.7% (73/363)	Figure 1, Jacobson et al. (2011)
BOC + PR*: RGT	Naïve	28 48	48.3% 22.3% (82/368)	Figure S1, Poordad et al. (2011)
PR	Naïve (GT1)	48	56.0% (202/361)	Figure 1, Jacobson et al. (2011)

PR	Naïve (GT4)	48	98.2% (107/109)	Figure 1, Kamal et al. (2011)
T12PR48	Experienced	48	62.4% (166/266)	Figure 1, Zeuzem et al. (2011)
PR	Experienced (GT1)	48	37.9% (50/132)	Figure 1, Zeuzem et al. (2011)
BOC + PR*: RGT	Experienced	36 48	29.3% 45.7% (74/162)	Figure S1, Bacon et al., 2011

BOC = boceprevir; PR = peg-IFN and ribavirin; RGT = response-guided therapy; SOF = sofosbuvir; T = telaprevir;.

*In these trials, we compute treatment duration for the DAA and the PR components separately, using data specified in the trial publication e.g., T12PR24 = 12 weeks of TPR and 24 or 48 weeks of PR. In SPRINT-2, treatment duration for PR within the BOC+PR response-guided therapy (RGT) regimen included a 4 week lead-in PR period (and corresponding discontinuations), as well as different treatment durations of the RGT-based PR following the lead-in period. This method of stratifying the components within a given regimen allows accurate computation of regimen costs.

Sources:

Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364(13):1207-17.

Kamal SM, Ahmed A, Mahmoud S, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Liver Int. 2011 Mar;31(3):401-11.

Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. N Engl J Med. 2011;364:2405-16.

Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection N Engl J Med. 2013;368:1878-87.

Poordad F, McCone J, Bacon BR, et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection. N Engl J Med. 2011;364:1195-1206.

Poynard T, Colombo M, Bruix J et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology. 2009;136(5):1618-28.e2.

Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364(25):2417-28.

Using the data from the two tables above, the expected days on therapy in a given trial arm is usually calculated using equation (1). For regimens where the treatment duration of its components differs for patients within a trial arm, we compute the expected treatment duration of each component individually. For example, in T12PR24, the expected treatment duration of TPR is calculated based on its 12-week duration (i.e., equation 1); whereas the expected treatment duration of PR is calculated based on a weighted average of those who received 24 weeks versus 48 weeks of PR therapy (i.e., equation 2). Computing regimen duration in this way is more accurate and prevents an overestimation of treatment costs, compared to an alternative methodology of simply multiplying the cost of a regimen by the average treatment duration of all its components.

In scenario analysis, we consider a situation where there are no dropouts, i.e., all patients complete the full course of therapy, as indicated in the treatments' respective SPC.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

It is expected that the drug costs of the intervention and the comparator regimens will be excluded from the Payment by Results tariff as they will be classified as high cost

drugs.

Resource identification, measurement and valuation studies

7.5.3 **Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources**

A systematic review of the literature was conducted to identify all resource use and unit cost data with potential relevance to the economic model. A recent systematic literature review undertaken by NICE, and reported by Hartwell et al., explored the same research question.[51] Therefore, the current review was carried out as an update of the NICE review, with the aim to identify studies that have been published since the systematic review by Hartwell et al 2011.

Since the Hartwell 2011 study focused on literature published up until 2009, the current review searched the following databases from 1st January 2009 to 2nd April 2014:

- MEDLINE (including MEDLINE In-Process)
- EMBASE
- EconLit
- NHS Economic Evaluation Database (EED)

Appendix 13 provides full details of the clinical keywords and medical subject headings used to search each database. A combined search was conducted to identify cost-effectiveness analyses and cost studies on healthcare resource use and unit costs associated with the management of CHC. The dataset was then used for the two reviews separately.

To be considered eligible for inclusion, studies had to meet pre-defined eligibility criteria developed based on the NICE Scope (Table 115).

Table 115: Protocol for systematic review of cost-effectiveness studies

Objective	To identify studies reporting resource use and unit costs associated with the management of adults with chronic hepatitis C in the UK, including treatment (ABT-450/ritonavir/ABT-267 and ABT-333 with or without RBV, peg-IFN + RBV, Telaprevir with peg-IFN + RBV, Boceprevir with peg-IFN + RBV), monitoring, progressive liver disease and adverse events.
Disease area	Chronic Hepatitis C
Patient population	Adults with genotype 1 chronic hepatitis C 3) who have not been previously treated

	4) in whom previous treatment has not resulted in a sustained virological response The following subgroups will be considered if evidence allows: c) Co-infection with HIV d) Response to previous treatment (non-response, partial response, relapsed) EXCLUDE: • Co-infection with chronic hepatitis B • People with substance dependence or illegal drug users
Country perspective	• Studies considering resource use from a UK perspective will be prioritized for inclusion. • If the search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources.
Interventions and comparators	Treatment with any of the below interventions. • ABT-450/ritonavir/ABT-267 in combination with ABT-333 • ABT-450/ritonavir/ABT-267 in combination with ABT-333 and ribavirin • Peginterferon-alfa and ribavirin • Telaprevir in combination with peginterferon alfa and ribavirin • Boceprevir in combination with peginterferon alfa and ribavirin
Study type	Inclusion criteria: • Cost-utility analyses (CUAs) • Cost-effectiveness analyses (CEAs) • Cost-benefit analyses (CBAs) • Cost-analyses (CAs) • Systematic reviews of economic evaluations and/or cost of illness analyses EXCLUDE: • Studies with a non-UK country perspective (see above criteria regarding “Country perspective”) if there are sufficient UK sources • Study reported only in conference proceeding, poster, or abstract format
Outcomes/information sought	Studies will be included if they report at least one of the primary outcomes of interest: • Resource use • Unit Costs o NHS Reference Costs & Payment by Results Tariff (including codes) o PSSRU costs o Expert opinion

	○ Other sources of cost estimates • Rationale for the choice of values used (in CEA and CUA models).
Literature databases	Using the OVID platform: • MEDLINE • MEDLINE In-process • EMBASE • EconLit Using the CRD platform: • NHS Economic Evaluations Database
Language	English only
Grey Literature	The following websites will be searched for completed or on-going studies and background material: • NICE HTAs
Search dates	From January 2009 to April 2014

The results of the search were exported to EndNote software and duplicates were removed. Titles and abstracts were reviewed by one reviewer according to the inclusion/exclusion criteria outlined in Table 115. Studies that did not meet inclusion criteria were rejected. Studies that appeared to meet inclusion criteria or that could not be excluded based on title and abstract alone were ordered for full text review. Figure 26 overleaf illustrates the study selection process using a PRISMA flow diagram:

Figure 26: PRISMA flow diagram of systematic review of cost-effectiveness studies

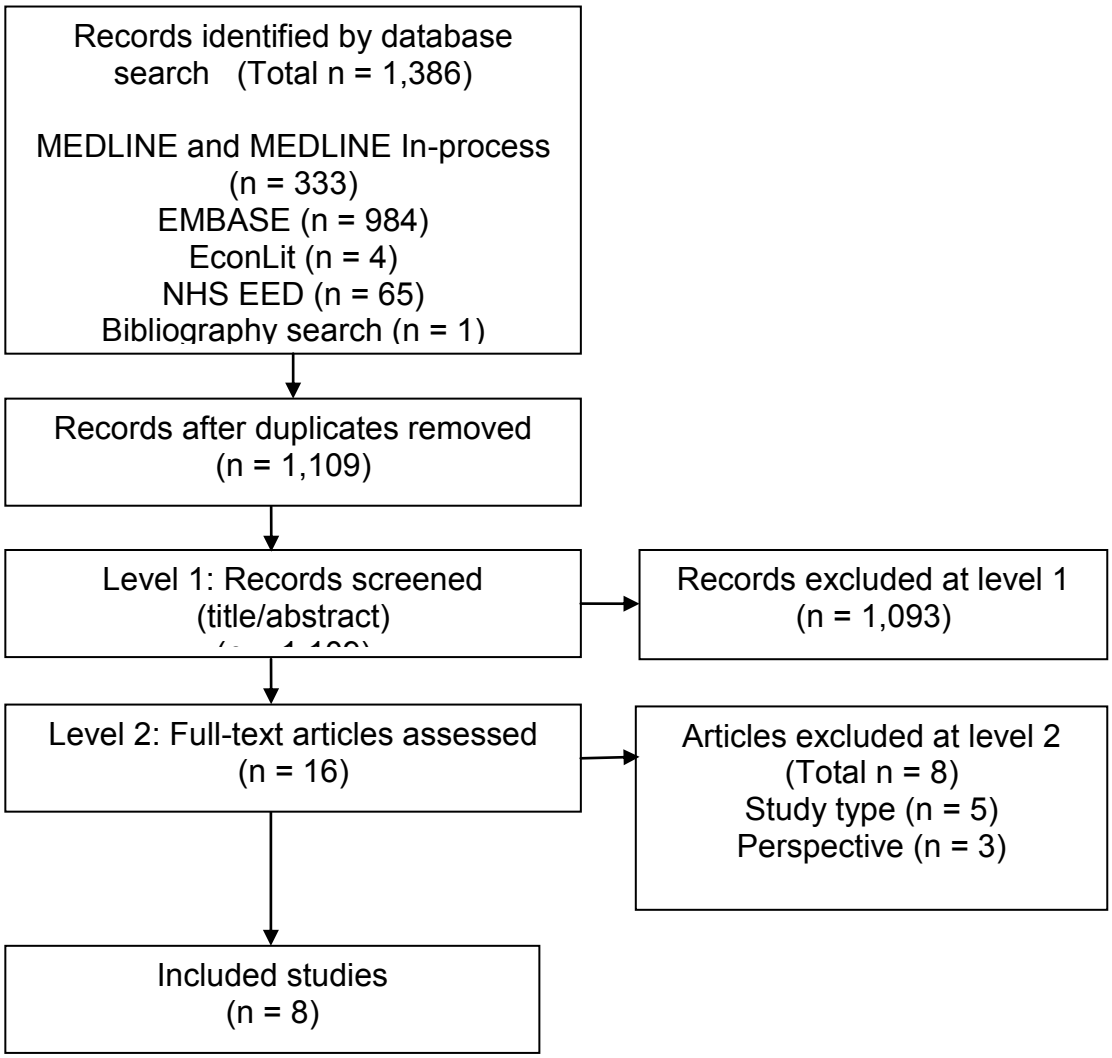


Table 116: Summary of included resource use studies based on cost-effectiveness analyses

Study	Perspective	Applicability[1]	Resource item	Costs (£)			Reference year	Source
Cost-effectiveness analyses								
Cure 2014[56]	England and Wales National Health Service (NHS)	Directly applicable	**Treatment**					
			Peg-IFN a2a (180ug/0.5mL /week)	124.40 per week			2011	BNF 2011 (13)
			RBV (1000 mg / week)	77.08 per week			2011	BNF 2011 (13)
			Telaprevir (750mg 3 x / day)	1,866.50 per week			2011	BNF 2011 (13)
			Boceprevir (800 mg / day)	2,800 per 28 days			2011	BNF 2011 (13)
			Health states					
			Mild - No treatment	175 (88 to 263)			2009/10	Hartwell 2011 (1)
			Mild - SVR following treatment	220 (110 to 329)			2009/10	Hartwell 2011 & Grishchenko 2009
			Mod. - No treatment	911 (455 to 1,366)			2009/10	
			Mod. - SVR following treatment	268 (134 to 403)			2009/10	Hartwell 2011 (1)
			Cirrhosis – No treatment	1,445 (723 to 2,169)			2009/10	Hartwell & Grishchenko
			Cirrhosis - SVR following treatment	475 (237 to 712)			2009/10	Hartwell 2011 (1)
			Decompensated cirrhosis	11,583 (5,791 to 17,374)			2009/10	Hartwell & Grishchenko
			Hepatocellular carcinoma	10,321 (5,161 to 15,482)			2009/10	Hartwell 2011 (1)
			Liver transplant	46,720 (23,360 to 70,080)			2009/10	Hartwell 2011 (1)
			Post-liver transplant	12,016			2009/10	Hartwell 2011 (1)
			Monitoring	Mild	Moderate	Cirrhosis		Hartwell 2011 (1)
			PR alone	867	867	928	2009/10	
			T/PR	971	971	1032	2009/10	Shepherd 2007 (7)
			B/PR	1033	1033	1094	2009/10	Shepherd 2007 (7)
			Adverse events					Shepherd 2007 (7)
			Rash	Not reported				Curtis 2010 (14)
			Pruritus	Not reported				Curtis 2010 (14)
			Nausea	Not reported				Curtis 2010 (14)
			Diarrhoea	Not reported				Curtis 2010 (14)
			Anemia	Not reported				Curtis 2010 (14)

Hartwell 2011[51] and Hartwell 2012[59]	England and Wales National Health Service (NHS)	Directly applicable	**On-treatment monitoring**			
			12 weeks	568	2007/08	
			16 weeks	600	2007/08	
			24 weeks	795	2007/08	
			48 weeks	1,473	2007/08	
			72 weeks	1,711	2007/08	
			Post-treatment surveillance			
			Non-responders	102	2007/08	
			Responders (SVR)	167	2007/08	
			Health states			
			Moderate CHC	843	2007/08	Shepherd 2007(7)
			CC	1,338	2007/08	Shepherd 2007(7)
			DC	10,725	2007/08	Shepherd 2007(7)
			HCC	9,557	2007/08	Shepherd 2007(7)
			Liver transplant, first year	43,263	2007/08	Shepherd 2007(7)
			Liver transplant, subsequent years	1,628	2007/08	Shepherd 2007(7)

McEwan 2013[60]	England and Wales National Health Service (NHS)	Directly applicable	**Treatment**			
			One week of peg-IFN a2a + RBV (assuming avg patient weight 79kg)	238	2010/11	BNF 2010(15)
			Health States			
			SVR (first year)	318	2003/04	Martin 2012(16)
			Chronic HCV (F0 state)	169	2003/04	Martin 2012(16)
			Chronic HCV (F1 state)	169	2003/04	Martin 2012(16)
			Chronic HCV (F2 state)	880	2003/04	Martin 2012(16)
			Chronic HCV (F3 state)	880	2003/04	Martin 2012(16)
			Chronic HCV (F4 state)	1,397	2003/04	Martin 2012(16)
			Decompensated cirrhosis	11,197	2003/04	Martin 2012(16)
			Hepatocellular carcinoma	9,978	2003/04	Martin 2012(16)
			Liver transplant (procedure)	33,555	2003/04	Martin 2012(16)
			Liver transplant (cost of care)	11,612	2003/04	Martin 2012(16)
			Liver transplant (subsequent years)	1,700	2003/04	Martin 2012(16)
			Monitoring			
			Initial consultation	1,424 (1,139 to 1,709)	2002/03	Shepherd 2004(17)
			Week 4	1,797 (1,437 to 2,156)	2002/03	Shepherd 2004(17)
			Week 6	1,829 (1,463 to 2,195)	2002/03	Shepherd 2004(17)
			Week 8	1,865 (1,491 to 2,237)	2002/03	Shepherd 2004(17)
			Week 12	2,121 (1,696 to 2,545)	2002/03	Shepherd 2004(17)
			Week 16	2,153 (1,722 to 2,584)	2002/03	Shepherd 2004(17)
			Week 24	2,186 (1,748 to 2,622)	2002/03	Shepherd 2004(17)
			Week 48	2,275 (1,820 to 2,730)	2002/03	Hartwell 2011(1)
			Week 72	2,540 (2,032 to 3,048)	2002/03	Hartwell 2011(1)

1. Applicability was assessed according to study setting, perspective, population, and intervention.

Table 117 Summary of included resource use studies

Study	Perspective	Study type and population	Population characteristics	Resource item	Costs (£)	Source
Aronld 2011[117]	England and Wales National Health Service (NHS)	Cost minimization analysis to determine the optimal strategy to diagnosis viral hepatitis.	People with at least one abnormal LFT and no known liver disease	**Liver function test** GP consultation to check LFT costs Receptionist check-in (2 minutes) Secretary time (1min) Phlebotomist time (5 minutes) Sample analysis: LFT Sample analysis: HB and HCsAg	 12.86 0.91 0.33 1.00 2.69 25.42	 MidReC 2009* MidReC 2009* MidReC 2009* MidReC 2009* UH Birmingham 2009* UH Birmingham 2009*
Backx 2014[118]	England and Wales National Health Service (NHS)	Retrospective case note review Patients with chronic HCV genotype 1 treated with peg-IFN a2a or a2b for a minimum of 2 months. Study entry was defined as the date of end of treatment with peg-IFN	Population characteristics were reported according to virological response to treatment and cirrhotic health state (see below)	**Unit costs** Outpatient clinic visit Outpatent clinical visit DNA HCV RNA test Ultrasound of abdomen or liver CT scan abdomen MRI scan liver Day case liver biopsy Ultrasound-guided biopsy Endoscopy Inpatient stay (per day) Critical care (per day) **Drug costs** Pegasys Viraferon PEG Copegus Rebetol	 194 50 75 79 141 245 322 348 142 252 815 124 160 13.21 9.56	 NHS PBR (URL NR) NHS PBR (URL NR) NHS PBR (URL NR) NHS PBR (URL NR) NHS PBR (URL NR) NHS PBR (URL NR) NHS PBR (URL NR) NHS PBR (URL NR) NHS PBR (URL NR) NHS PBR (URL NR) NHS PBR (URL NR) BNF (year NR) BNF (year NR) BNF (year NR) BNF (year NR)

Study	Perspective	Study type and population	Population characteristics	Resource item	Costs (£)			Source
		and RBV.	SVR	SVR	Chronic	Cirrhosis	Decomp	
			Total N = 108	No. of patients per disease state	100	6	2	Current study
			Age = 40.5	Follow-up years	351.6	26.1	4.4	Current study
			(±9.7)	Clinic visits (n)	77	52	12	Current study
			64.8% male	Per patient/year	0.22	1.99	2.73	Current study
			Infection	Clinic DNAs	28	6	1	Current study
			duration = 18.2	Per patient/year	0.08	0.23	0.23	Current study
			(10.1 years)	Ultrasound scans (n)	0	28	4	Current study
			Ishak 0/1/2	Per patient/year	0	1.07	0.91	Current study
			66.7%	CT scans (n)	0	0	0	Current study
			Ishak 3/4	MRI scans (n)	0	0	0	Current study
			20.3%	HCV tests (n)	32	20	3	Current study
			Ishak 13.0%	Per patient/year	0.09	0.77	0.7	Current study
				Day-case visits (n)	1	3	0	Current study
				Inpatient stay (days)	0	0	0	Current study
				Costs	58 (45 – 75)	586 (207 – 1655)	719 (119-4,347)	Current study
			Non-SVR	Non-SVR	Chronic	Cirrhosis	Decomp	
			Total N = 85	No. of patients per disease state	54	27	10	Current study
			Age = 48.0	Follow-up years	197.3	103.1	17.4	Current study
			(±9.4)	Clinic visits (n)	409	234	63	Current study
			64.7% male	Per patient/year	2.07	2.30	3.63	Current study
			Infection	Clinic DNAs	53	40	2	Current study
			duration = 22.7	Per patient/year	0.23	0.39	0.12	Current study
			(9.9 years)	Ultrasound scans (n)	37	99	13	Current study
			Ishak 0/1/2	Per patient/year	0.19	0.96	0.75	Current study
			52.0%	CT scans (n)	2	16	2	Current study
			Ishak 3/4	MRI scans (n)	0	2	5	Current study
			19.2%	HCV tests (n)	79	26	2	Current study
			Ishak 28.8%	Per patient/year	0.04	0.25	0.12	Current study

Study	Perspective	Study type and population	Population characteristics	Resource item	Costs (£)			Source
				Day-case visits (n) Inpatient stay (days) Costs	21 6 589 (417 – 833)	27 14 914 (560 to 1,491)	5 57 4,364 (1,951 to 9,757)	Current study Current study Current study
Foxton 2010[119]	England and Wales National Health Service (NHS)	Retrospective analysis of resource use	Adult patients registered with UK Transplant who underwent liver transplantation for chronic liver disease at King's College Hospital between 2000 and 2003. Results reported according to	**Meld <11** Post LT ICU stay Post LT hospital stay Cost **Meld 11-18** Post LT ICU stay Post LT hospital stay Cost **Meld 19-24** Post LT ICU stay Post LT hospital stay Cost **Meld >24** Post LT ICU stay Post LT hospital stay Cost	2 (1-4) days 18 (13-30) days £3,600 (IQR: £1,800 to £5,400) 1 (1-5) days 20 (14 – 36) days £3,600 (IQR: £1,800 – £7,200) 3 (1-8) days 23.5 (17-39) days £5,400 (£1,800-£14,400) 8 (2-20) days 23.5 (20-42) days £12,024 (£4,050 - £51,570)			Current study Current study Current study Current study Current study Current study Current study Current study Current study Current study Current study Current study

Study	Perspective	Study type and population	Population characteristics	Resource item	Costs (£)	Source
			patient MELD score at transplantation			
Thorlund 2012[120]	England and Wales National Health Service (NHS)	Budget impact analysis	Treatment naïve and treatment experienced patients with chronic HCV genotype 1	**Drug costs**		
				Boceprevir	£700 per week	MIMS Online (22)
				Telaprevir	£1866 per week	MIMS Online (22)
				Peg-IFN a2a	£124 per week (80.7% market share)	MIMS Online (22)
				Peg-IFN a2b	£199 per week (19.3% market share)	MIMS Online (22)
				Ribavirin (Copegus)	£92 per week (70.1% market share)	MIMS Online (22)
				Ribavirin (Rebetol)	£67 per week (29.9% market share)	MIMS Online (22)
				Monitoring		
				Average cost per week	£32 per week	Clinical experts
				Clinic visit (monthly)	£40	Clinical experts
				Blood test (monthly)	£100	Clinical experts
				Adverse events		
				Anaemia management	£869	Clinical experts
				Clinic visit (Initial and follow-up)	£25	Clinical experts
				Erythropoietin treatment (20% of anaemia patients)	£250	Clinical experts
				Blood transfusion (5% of patients)	£400	Clinical experts
				Neutropenia management	£25/patient treated	Clinical experts
				Clinic visit (Initial)	£25	Clinical experts
				Rash management	£155/patient treated	Clinical experts
				Clinic visit (Initial and follow-up)	£25	Clinical experts
				Dermatologist visit	£75	Clinical experts
				Hydrocortisone 1% cream (2 month supply)	£30	Clinical experts

Study	Perspective	Study type and population	Population characteristics	Resource item	Costs (£)	Source
				Pruritus management Clinic visit (Initial and follow-up) Dermatologist visit Atarax (25mg capsules, 2 month supply)	£165/patient treated £25 £75 £50	

*Source not cited.

7.5.4 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:**

As described in section 7.3.5, AbbVie conducted advisory board meetings to test, validate and refine assumptions and decisions made within the cost-effectiveness model. For further details, please refer to section 7.3.5.

Intervention and comparators' costs

7.5.5 **Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

Unit costs for the comparator regimens were sourced from MIMS 2014 and are reported in Table 118 below. Please note that the cost of AbbVie's regimens will be confidential until the time of commercial launch.

Table 118: Unit costs associated with the technology in the economic model

Compound	Drug name	Price (2013/14)	Cost per dose	Cost per day	Cost Source
AbbVie 3D	Viekirax and Exviera	£11,666.66 for 28 day's supply of Viekirax (56 tablets) and Exviera (56 tablets)	**£416.67**	**£416.67**	AbbVie data on file
AbbVie 2D	Viekirax	£10,733.33 for 28 day's supply of Viekirax (56 tablets)	**£383.34**	**£383.34**	AbbVie data on file
Sofosbuvir	Sovaldi	£11,660 for 28 400mg tablets	£416.43	£416.43	MIMS 2014
Simeprevir		£266.64 for 150mg tablet	£266.64	£266.64	MIMS 2014
Boceprevir	Victrelis	£2,800 for 336 200mg capsules	£8.33	£100.00	MIMS 2014
Telaprevir	Incivo	£1,866.50 for 42 375mg tablets	£44.44	£266.64	MIMS 2014
Peg-IFN alfa-2a 80.7% market share*	Pegasus	£497.60 for 4 180ug syringes	£124.40	£19.84	

Peg-IFN alfa-2b 19.3% market share*	ViraferonPEG	£199.38 for 150ug syringe	£199.38		
Ribavirin 70.1% market share*	Copegus	£92.50 for 42 200mg tablets	£2.20	£10.58	MIMS 2014
		£369.98 for 168 200mg tablets	£2.20		
		£246.65 for 112 200mg tablets	£2.20		
		£246.65 for 56 400mg tablets			
Ribavirin 29.9% market share*	Rebetol	£160.69 for 84 200mg capsules	£1.91		
		£267.81 for 140 200mg capsules	£1.91		
		£321.38 for 168 200mg capsules	£1.91		

*Where more than one drug was available, market share estimates were based on UK budget impact analysis by Thorlund et al., 2012[120]

As mentioned in section 7.5.1, total treatment cost is a function of the regimen's unit cost and the mean treatment duration estimated for all regimen components directly from the trials (further described in section 7.5.1). Based on the AbbVie 3D example in GT1 treatment-naïve patients, Table 119 illustrates the way the total costs were estimated for each regimen. We further describe the method below.

In our model, outcomes for GT1 patients such as treatment duration are estimated as a weighted average between the outcomes observed for GT1a and GT1b patients based on AbbVie clinical trials. Thus, the total treatment duration for GT1a and GT1b is comprised of the trial treatment duration of mild/moderate and cirrhosis patients respectively and is further weighted by the assumed distribution of these health states in the following manner:

*DAA Duration in Days (Trial) for GT1a patients =((shr_mild+shr_moderate)*83.3)+(shr_CC*163.6) = 91.4 days*

*RBV Duration in Days (Trial) for GT1a patients =((shr_mild+shr_moderate)*83.3)+(shr_CC*163.6) = 91.4 days*

*DAA Duration in Days (Trial) for GT1b patients =((shr_mild+shr_moderate)*83.8)+(shr_CC*83.2) = 83.7 days*

RBV Duration in Days (Trial)
*for GT1b patients =((shr_mild+shr_moderate)*0)+(shr_CC*83.2) = 8.3 days*

Where,
shr_mild and shr_moderate = share of mild and moderate patients at model entry
shr_CC = share of CC patients at model entry

DAA duration in Days (Trial) for
*GT1 patients (all fibrosis stages) = (shr_gen1a*91.4) + ((1-shr_gen1a*83.7) = 89 days*

RBV duration in Days (Trial) for
*GT1 patients (all fibrosis stages) = (shr_gen1a*91.4) + ((1-shr_gen1a*8.3) = 65 days*

The same methodology is used to estimate average treatment duration for all comparator regimens. For further details, please refer to the cost-effectiveness model.

Table 119: Base-case treatment duration for AbbVie 3D regimen, GT1, IFN-eligible, treatment-naïve patients

Regimen					DAA				Ribarvin			
Patient Segment, Genotype, Fibrosis Stage, Trial arm	Trial	No of Patients who Received ≥1 dose of study drugs	N* Tx Compl	N^ Tx Discont	Weeks* Tx Compl	Weeks^ Tx Discont	Duration Days, No Dropouts	Duration# Days (Trial)	Weeks* Tx Compl	Weeks^ Tx Discont	Duration Days, No Dropouts	Duration Days (Trial)
Naïve IFN E GT1a No cirrhosis 3D+RBV 12 weeks	SAPPHIRE I PEARL IV**	573	564	9	12.0	6.0	84.0	83.3	12.0	6.0	84.0	83.3
Naïve IFN E GT1a Cirrhosis 3D+RBV 24 weeks	TURQUOISE II	172	163	9	24.0	12.0	168	163.6	12.0	6.0	168	163.6
Naïve IFN E GT1b No cirrhosis 3D 12 weeks	PEARL III	209	208	1	12.0	6.0	84.0	83.8	0.0	0.0	0.0	0.0
Naïve IFN E GT1b Cirrhosis 3D+RBV	TURQUOISE II	208	204	4	12.0	6.0	84.0	83.2	12.0	6.0	84.0	83.2

12 weeks

*Compl = completed; ^Discont = discontinued; # example: **Duration Days (Trial) = ((564/573*12) + (9/573*6)) * 7**
** We add the number of patients (Ns) who received at least one dose of study drugs/completed treatment/discontinued treatment from SAPPHIRE I and PEARL IV to create composite numbers. We use these composite Ns to compute treatment duration for GT1a naive patients.

Further, protocols describing the frequency of monitoring of patients whilst being treated with peginterferon were developed for previous assessment by Shepherd et al., 2007 based on clinical practice at Southampton University Hospital Trust. These protocols were subsequently referenced by Hartwell et al., 2011 and in other NICE submissions. Consistent with previous assessments in chronic Hepatitis C, our submission also references these assumptions regarding the intensity and quantities of resources associated with patient monitoring when on PegIFN-based regimens. These assumptions were further adapted for novel DAA regimens to either reflect shortened treatment duration of PegIFN-containing therapy (SOF+PR) or treatment with a PegIFN-free regimen (3D or 2D). The adapted assumptions were validated during the previously described advisory board (see section 7.3.5). All unit costs reported by Shepherd 2007 were cross-checked against other available sources, including results of the systematic review of resource use estimates and other relevant NICE assessments (particularly the NICE hepatitis B guideline). In addition, where Shepherd unit costs were used, PSSRU inflation indices reported by Curtis 2013 were then used to inflate 2006/7 values to 2012/13 prices.

A detailed breakdown of the resource use and unit costs is provided in Table 120, with monitoring costs summary provided in and Table 121 below.

Table 120: Breakdown of monitoring costs during the year of treatment

DETAILED BREAKDOWN

Resource item (Shepherd 2007)	Unit cost (Shepherd 2006/07)	Unit cost (2012/13)	Unit cost source
BASELINE			
1st treatment appointment			
Time with nurse - 120 minutes (Grade H assumed)	£33.13	£116.00	PSSRU 2013 Community nurse advanced, band 7 (equivalent to grade H), 2 x cost per hour including qualifications
Time with doctor - 10 minutes (consultant assumed)	£7.72	£23.17	PSSRU 2013 Hospital consultant medical, (1/6) x cost per hour including qualifications
Overheads for clinic administration (pulling notes etc.)	£3.58	£4.14	Inflated using PSSRU 2013 HCHS inflation indices
Staff costs for outpatient appointment	£44.43	£143.31	Sum
Full blood count	£2.20	£2.55	Inflated using PSSRU 2013 HCHS inflation indices
Internal normalized ratio	£2.40	£2.78	Inflated using PSSRU 2013 HCHS inflation indices
Urea &	£5.60	£6.48	2006/2007 costs inflated using PSSRU 2013 HCHS

Electrolytes			inflation indices. Note this differs from the CHB guideline cost (0.80) - used the Shepherd cost as it is closer to that reported by Wright 2006
Liver function tests	£3.60	£1.03	2013 NICE HBV Guideline - based on expert opinion
HCV quantitative viral load	£152.27	£40.00	2013 NICE HBV Guideline - based on expert opinion in consultation with UK laboratory managers (assumes PCR)
Pregnancy test (5% of patients)	£0.25	£0.29	Inflated using PSSRU 2013 HCHS inflation indices
Total for baseline treatment appointment	£210.75	£196.43	Sum
Subsequent appointments			
Basic checks (weeks 1, 2, 6, with pregnancy test at weeks 16 + 20)			
Time with nurse - 30 minutes (Grade H assumed)	£8.28	£29.00	PSSRU 2013 Community nurse advanced, band 7 (equivalent to grade H), 0.5 x cost per hour including qualifications
Time with doctor - 5 minutes (consultant assumed)	£3.86	£11.58	PSSRU 2013 Hospital consultant medical, (5/60) x cost per hour including qualifications
Overheads for clinic administratio n (pulling notes etc.)	£3.58	£4.14	Inflated using PSSRU 2013 HCHS inflation indices
Staff costs	£15.72	£44.73	Sum
Full blood count	£2.20	£2.55	Inflated using PSSRU 2013 HCHS inflation indices
Urea & Electrolytes	£5.60	£6.48	Inflated using PSSRU 2013 HCHS inflation indices. Note this differs from the cost listed in the Hepatitis B guideline (0.80). The value reported by Shepherd was used in preference as it is closer to that reported by Wright 2006.
Liver function tests	£3.60	£1.03	2013 NICE HBV Guideline - based on expert opinion
Pregnancy test (weeks 16 + 20)	£0.25	£0.29	Inflated using PSSRU 2013 HCHS inflation indices
Total for each basic assessment	£27.37	£55.07	Sum

More detailed assessment (at weeks 4)			
Time with nurse - 30 minutes (Grade H assumed)	£8.28	£29.00	PSSRU 2013 Community nurse advanced, band 7 (equivalent to grade H), 0.5 x cost per hour including qualifications
Time with doctor - 5 minutes (consultant assumed)	£3.86	£11.58	PSSRU 2013 Hospital consultant medical, (5/60) x cost per hour including qualifications
Overheads for clinic administratio n (pulling notes etc.)	£3.58	£4.14	Inflated using PSSRU 2013 HCHS inflation indices
Staff costs	£15.72	£44.73	Sum
Full blood count	£2.20	£2.55	Inflated using PSSRU 2013 HCHS inflation indices
Urea & Electrolytes	£5.60	£6.48	Inflated using PSSRU 2013 HCHS inflation indices. Note this differs from the cost listed in the Hepatitis B guideline (0.80). The value reported by Shepherd was used in preference as it is closer to that reported by Wright 2006.
Liver function tests	£3.60	£1.03	2013 NICE HBV Guideline - based on expert opinion. This is the cost of ONE test.
Internal normalized ratio (blood clotting)	£2.40	£2.78	Inflated using PSSRU 2013 HCHS inflation indices
Pregnancy test (5% of patients)	£0.25	£0.29	Inflated using PSSRU 2013 HCHS inflation indices
HCV quantitative viral load	£152.27	£40.00	2013 NICE HBV Guideline - based on expert opinion in consultation with UK laboratory managers (assumes PCR)
Total for week 4	£182.04	£97.85	Sum

More detailed assessment (at weeks 8)			
Time with nurse - 30 minutes (Grade H assumed)	£8.28	£29.00	PSSRU 2013 Community nurse advanced, band 7 (equivalent to grade H), 0.5 x cost per hour including qualifications
Time with doctor - 5 minutes (consultant assumed)	£3.86	£11.58	PSSRU 2013 Hospital consultant medical, (5/60) x cost per hour including qualifications
Overheads for clinic administratio n (pulling notes etc.)	£3.58	£4.14	Inflated using PSSRU 2013 HCHS inflation indices

Staff costs	£15.72	£44.73	Sum
Full blood count	£2.20	£2.55	Inflated using PSSRU 2013 HCHS inflation indices
Urea & Electrolytes	£5.60	£6.48	Inflated using PSSRU 2013 HCHS inflation indices. Note this differs from the cost listed in the Hepatitis B guideline (0.80). The value reported by Shepherd was used in preference as it is closer to that reported by Wright 2006.
Liver function tests	£3.60	£1.03	2013 NICE HBV Guideline - based on expert opinion. This is the cost of ONE test.
Internal normalized ratio (blood clotting)	£2.40	£2.78	Inflated using PSSRU 2013 HCHS inflation indices
Pregnancy test (5% of patients)	£0.25	£0.29	Inflated using PSSRU 2013 HCHS inflation indices
Total for week 8	£29.77	£57.85	Sum

Detailed assessment (week 12)			
Time with nurse - 30 minutes (Grade H assumed)	£8.28	£29.00	PSSRU 2013 Community nurse advanced, band 7 (equivalent to grade H), 0.5 x cost per hour including qualifications
Time with doctor - 10 minutes (consultant assumed)	£7.72	£23.17	PSSRU 2013 Hospital consultant medical, (1/6) x cost per hour including qualifications
Overheads for clinic administratio n (pulling notes etc.)	£3.58	£4.14	2006/2007 costs inflated using PSSRU 2013 HCHS inflation indices
Staff costs	£19.58	£56.31	Sum
Full blood count	£2.20	£2.55	2006/2007 costs inflated using PSSRU 2013 HCHS inflation indices
Urea & Electrolytes	£5.60	£6.48	2006/2007 costs inflated using PSSRU 2013 HCHS inflation indices. Note this differs from the CHB guideline cost (0.80) - used the Shepherd cost as it is closer to that reported by Wright 2006
Liver function tests	£3.60	£1.03	2013 NICE HBV Guideline - based on expert opinion
Internal normalized ratio (blood clotting)	£2.40	£2.78	2006/2007 costs inflated using PSSRU 2013 HCHS inflation indices
TFT (thyroid function tests)	£13.30	£4.94	2005/06 costs reported in Shepherd 2006 inflated using PSSRU 2013 HCHS inflation indices. This cost was chosen as it more closely matched that reported by Shepherd 2006, Wright 2006, and was recently validated by experts on the Hepatitis B guideline group.
Alpha	£1.31	£1.52	2006/2007 costs inflated using PSSRU 2013 HCHS

fetoprotein (cirrhotic patients - 15%)			inflation indices
HCV quantitative viral load	£152.27	£40.00	2013 NICE HBV Guideline - based on expert opinion in consultation with UK laboratory managers (assumes PCR)
Pregnancy test (5% of patients)	£0.25	£0.29	Inflated using PSSRU 2013 HCHS inflation indices
Total for week 12	£200.51	£115.89	Sum
Detailed assessment (week 24)			
Time with nurse - 30 minutes (Grade H assumed)	£8.28	£29.00	PSSRU 2013 Community nurse advanced, band 7 (equivalent to grade H), 0.5 x cost per hour including qualifications
Time with doctor - 15 minutes (consultant assumed)	£11.59	£34.75	PSSRU 2013 Hospital consultant medical, (15/60) x cost per hour including qualifications
Overheads for clinic administratio n (pulling notes etc.)	£3.58	£4.14	Inflated using PSSRU 2013 HCHS inflation indices
Staff cost	£23.45	£67.89	Sum
Full blood count	£2.20	£2.55	Inflated using PSSRU 2013 HCHS inflation indices
Urea & Electrolytes	£5.60	£6.48	Inflated using PSSRU 2013 HCHS inflation indices. Note this differs from the CHB guideline cost (0.80) - used the Shepherd cost as it is closer to that reported by Wright 2006
Liver function tests	£3.60	£1.03	2013 NICE HBV Guideline - based on expert opinion
Internal normalized ratio (blood clotting)	£2.40	£2.78	Inflated using PSSRU 2013 HCHS inflation indices
TFT (thyroid function tests)	£13.30	£4.94	2005/06 costs reported in Shepherd 2006 inflated using PSSRU 2013 HCHS inflation indices. This cost was chosen as it more closely matched that reported by Shepherd 2006, Wright 2006, and was recently validated by experts on the Hepatitis B guideline group.
Alpha fetoprotein (cirrhotic patients - 15%)	£1.31	£1.52	Inflated using PSSRU 2013 HCHS inflation indices
HCV qualitative viral load	£11.33	£6.00	2013 NICE HBV Guideline - based on expert opinion in consultation with UK laboratory managers (assumes PCR)

Liver ultrasound	£7.20	£79.00	Backx 2014
Pregnancy test (5% of patients)	£0.25	£0.29	Inflated using PSSRU 2013 HCHS inflation indices
HCV quantitative viral load	£152.27	£40.00	2013 NICE HBV Guideline - based on expert opinion in consultation with UK laboratory managers (assumes PCR)
Total for week 24	£222.91	£212.48	Sum

Table 121: Summary of on treatment monitoring costs by duration of treatment

SUMMARY	Unit costs (2012/13)
Cost per patient treated with 3D for 12 weeks	
First treatment assessment	£196.43
Week 4 assessment	£97.85
Week 8 assessment	£57.85
Week 12 assessment	£115.89
Total	**£468.03**
Cost per patient treated with Sofosbuvir for 12 weeks	
First treatment assessment	£196.43
Week 4 assessment	£97.85
Week 8 assessment	£57.85
Week 12 assessment	£115.89
Total	**£468.03**
Cost per patient treated with DAA + IFN for 24-weeks	
First treatment assessment	£196.43
Basic assessments at weeks 1,2,6,16, and 20	£275.37
Week 4 assessment	£97.85
Week 8 assessment	£57.85
Week 12 assessment	£115.89
Week 24 assessment	£212.48
Total	**£955.87**
Cost per patient treated with DAA + IFN for 28-weeks	
First treatment assessment	£196.43
Basic assessments at weeks 1,2,6,16, and 20	£275.37
Week 4 assessment	£97.85
Week 8 assessment	£57.85
Week 12 assessment	£115.89
Week 24 assessment (replaced by 28 weeks assessment)	£0.00
Week 28 assessment (as per week 24 assessment)	£212.48
Total	**£955.87**
Cost per patient treated with DAA + IFN for 36-weeks	

First treatment assessment	£196.43
Basic assessments at weeks 1,2,6,16, and 20	£275.37
Week 4 assessment	£97.85
Week 8 assessment	£57.85
Week 12 assessment	£115.89
Week 24 assessment	£212.48
Week 28 assessment (replaced by week 36 assessment)	£0.00
Week 36 (as per week 12)	£115.89
Total	**£1,071.77**
Cost per patient treated with DAA + IFN for 48-weeks	
First treatment assessment	£196.43
Week 4 assessment	£97.85
Week 8 assessment	£57.85
Week 12 assessment	£115.89
Week 24 assessment	£212.48
Basic assessments at weeks 28, 32, 40 and 44	£220.29
Week 36 (as week 12, excluding viral load)	£75.89
Week 48 (as week 24 excluding viral load)	£172.48
Total	**£1,424.54**

As highlighted in the table above, monitoring costs vary according to treatment duration (described in the paragraphs above and further reported in Table 121). As a consequence of the complexity of treatment regimens assessed in our submission driven by the different response-guided rules and protocols with respect to the use of lead-in phases and different timing for measuring virologic response, we have decided to simplify the monitoring costs. For example, we assume that patients treated for 28 weeks on average incur the same monitoring costs as those treated for 24 weeks. 28-weeks monitoring cost in our base case applies to treatment naïve patients treated with TPR+PR as the "PR tail" averages out to 28 weeks (198 days) for patients treated with either 24 or 48 weeks. As described in the ADVANCE trial (see section 7.3.1), in the T12PR group, the total duration of treatment was either 24 or 48 weeks. A treatment rule was employed based on extended rapid virologic response whereby patients who met the response criteria received additional 12 weeks of PR alone, leading to total treatment duration of 24 weeks. Patients who did not meet the criteria received additional 36 weeks of treatment with PR, leading to total treatment duration of 48 weeks. Therefore by applying 24 weeks' worth of monitoring costs to all treatment naïve patients irrespective of their overall treatment duration, we have underestimated total monitoring costs for patients treated for 48 weeks as they are bound to incur additional monitoring costs beyond 28 weeks.

Further, we assume the same monitoring costs for AbbVie's regimen and for SOF+PR 12 week regimen despite the fact that AbbVie's regimen is IFN-free and is thus anticipated to be associated with far less monitoring than the IFN-based regimens. However we decided to be conservative in recognizing that during early stages of therapy adoption, patients may be monitored more often than they will be in the future. As a result, we assume the same monitoring costs for 3D/2D and for SOF+PR.

For further summary, please see Table 122 below:

Table 122: Monitoring costs per treatment

Item	Annual Cost (2012/13)
On-treatment monitoring	
12 weeks AbbVie regimen therapy	£468.03
24 weeks AbbVie regimen therapy	£936.06
12 weeks of sofosbuvir + PR therapy	£468.03
24 weeks of sofosbuvir + PR therapy	£936.06
24 weeks (168 days) of therapy (T or B + PR)	£955.87
28 weeks (198 days) therapy (T or B + PR)	£955.87
36 weeks (252 days) therapy (T or B + PR)	£1,071.77
48 weeks (336 days) of therapy (T or B + PR)	£1,424.54

Health-state costs

7.5.6 **Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.**

The costs associated with HCV infected patients in each health state were obtained from two sources. Costs reported by Hartwell et al., 2011 informed our health state costs for mild chronic HCV, DCC, HCC (first and subsequent years), liver transplant (first and subsequent years). All costs are updated to current values using the PSSRU pay and prices inflation index (Curtis 2013). A retrospective chart review of patients with CHC was identified in our systematic review of resource use literature. Study by Backx 2014 evaluated resource use among HCV patients according to their response to treatment and is deemed to represent a more recent and relevant source than Hartwell et al., 2011 for patients occupying moderate fibrosis, compensated cirrhosis and all recovered (SVR) health states. The same costs are applied to treatment naïve and treatment experienced patients as well as patients with GT1 or GT4.

A summary of health state costs is outlined below.

Table 123: 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

It is conservatively assumed that all recovered patients require life-long monitoring post achieving an SVR, irrespective of their initial fibrosis stage.

Adverse-event costs

7.5.7 **Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

Frequencies of AEs for each regimen were previously described in section 7.3.1. We obtain the resource use and unit cost for the key treatment-related adverse events from a recent UK budget impact analysis by Thorlund 2012[120] and expert opinion. Table 124 below indicates the average cost per patient who experiences each adverse event. Assumptions used to inform the cost of depression treatment and monitoring were obtained from NICE GC 90: Depression in adults.

Table 124: Resource use and unit costs associated with treatment-related AEs

Event	Resource use	Cost (2012/13)	Source
Anemia			
Clinic visit	2 (initial and follow-up)	£26.00	Thorlund 2012
Erythropoetin treatment	20% of anemia patients for 8 weeks	£256.00	Thorlund 2012
Blood transfusion	5% of anemia patients	£409.00	Thorlund 2012
Average per patient treated for anemia		£482.05	Sum
Depression			

Clinic visit (moderate depression (50%) treated in primary care)	5 (2 initial and every 2 months thereafter for a total of 8 months)	£26.00	NICE GC90
Outpatient visit (severe depression (50%) treated in specialist setting)	5 (2 initial and every 2 months thereafter for a total of 8 months)	£130.00	NICE GC90
Antidepressant treatment	8 months citalopram	£0.22 per week	Gao 2012; NICE GC90
Average per patient treated for depression		£397.63	
Rash			
Clinic visit	2 (initial and follow-up)	£26.00	Thorlund 2012
Dermatologist visit	1	£77.00	Thorlund 2012
Hydrocortisone 1% cream	2 month supply	£31.00	Thorlund 2012
Average per patient treated for rash		£160.00	Sum

Cost of neutropenia	
Item	Cost
Cost of treatment	£486
Cost of outpatient visit	£348
Cost of consultant visit	£108
Total event cost	**£942**
Source: pg 230-233, Table 64-67; Sofosbuvir NICE manufacturers submission	

Cost of thrombocytopenia	
Cost item	Cost
Cost of treatment	£385
Cost of outpatient visit	£348
Cost of consultant visit	£108
Total event cost	**£841**
Source: pg 230-233, Table 64-67; Sofosbuvir NICE manufacturers submission	

Miscellaneous costs

7.5.8 **Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.**

Not applicable.

7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Uncertainty around structural assumptions was tested in the model. We conducted three types of sensitivity analyses: various scenario analyses described directly below, deterministic sensitivity analysis (DSA described in section 7.6.2) and probabilistic sensitivity analysis (PSA described in section 7.6.3). Table 125 below lists scenario analyses which have been conducted to explore sensitivity of the results to some key assumptions made in the model.

Table 125: Variables that were tested in scenario analyses

Variable	Base Case Value	Scenario, Low	Scenario, High, where applicable	Notes
Baseline patient characteristics, treatment-naïve				
Initial fibrosis distribution				
Mild	46.0%	100.0%	0.0%	Extreme values testing
Moderate	44.0%	0.0%	0.0%	
CC (chronic HCV)	10.0%	0.0%	100.0%	Extreme values testing
Age (in years)	40.0	35.0	55.0	Standard deviation assumed
Male	70.0%	65.0%	75.0%	
%GT1a	58.8%	50.0%		
Baseline patient characteristics, treatment-experienced				
Initial fibrosis distribution				
Mild	33.0%	100.0%	0.0%	Mild fibrosis only subgroup analysis
Moderate	35.0%	0.0%	0.0%	
CC (chronic HCV)	32.0%	0.0%	100.0%	Cirrhotic only subgroup analysis
Age (in years)	45.0	35.0	55.0	Standard deviation assumed
Male	70.0%	65.0%	75.0%	
%GT1a	58.8%	50.0%		Assume 50:50 split between GT1a and GT1b
Time horizon	70 years	30 years		Assume shorter time horizon
Discount rates				
Costs	3.5%	0.0%	6.0%	
Health Utilities	3.5%	0.0%	6.0%	
LYGs	3.5%	0.0%	6.0%	

Treatment duration	Trial-based discontinuation	No dropout	See Section 7.5
AbbVie Regimen			
SVR	SVR not stratified by mild/moderate fibrosis	SVR stratified by mild/ moderate fibrosis	
%GT1a naïve cirrhotic patients treated for 12 weeks*	[redacted]	[redacted]	[redacted]
%GT1a experienced cirrhotic patients treated for 12 weeks*	[redacted]	[redacted]	[redacted]
SOF + PR: %GT1 naïve cirrhotics treated with[Ω]			Scenario analysis as per SOF+PR SPC
12 weeks **24 weeks**	100% 0%	20% 80%	
SVR with PR			
GT1: Hadziyannis et al. (2004)			Base case: ADVANCE PR48; ERG suggestion
Mild	45.6%	56.0%	
Moderate	43.5%	56.0%	
CC	33.3%	38.0%	
GT1: McHutchinson et al. (2009)			Base case: ADVANCE PR48; ERG suggestion
Mild	45.6%	43.6%	
Moderate	43.5%	43.6%	
CC	33.3%	23.6%	
GT4: Yee et al. (2014)			Base case: Kamal et al. (2011)
Mild/Moderate	70.6%	61.3%	
Grishchenko et al. (2009)			Base case: Shepherd et al. (2007)
Mild to moderate, age at treatment			
30 Years	0.025	0.015	
40 Years	0.025	0.023	
50 Years	0.025	0.035	
Moderate to CC, age at treatment			
30 Years	0.037	0.021	
40 Years	0.037	0.032	
50 Years	0.037	0.048	
Indirect costs (Yes/No)	No	Yes	See text below
SVR-related utility increment			Base case: Hartwell et al.

			(2011)
Vera-Llonch et al. (2013)	+ 0.05	+4.56%	See text below
AbbVie trial	+ 0.05	varies	See text below

*Proportion of GT1a cirrhotic patients with all three favourable baseline laboratory values (AFP < 20 ng/mL, platelets ≥ 90 x 109/L, and albumin ≥ 35 g/L). We compute this proportion using AbbVie clinical trial data, to weight the clinical inputs (and thus outcomes) between patients receiving 12 vs 24 weeks of patients in scenario analysis.

Ω Scenario where 80% of treatment-naïve cirrhotic patients treated with SOF+ PR will be treated for 24 weeks, while 20% are treated for 12 weeks: due to the absence of clinical data, we do not vary SVR, AE rates, completion rates and on-treatment disutility between patients treated with 12 vs 24 weeks of SOF + PR. In this scenario, we vary: 1. regimen duration (and thus total cost of regimen); and 2. monitoring costs

Baseline patient characteristics

Baseline characteristics of the modelled cohorts were sourced from Hartwell et al. 2011 and Shepherd et al. 2007 studies reporting relevant characteristics for the UK population of patients with chronic hepatitis C. However the impact of the assumed patient characteristics (namely age, proportion male and proportion of patients with GT1a) on the model results was tested using alternative assumptions reported in the table above.

Scenario analysis on indirect costs in the model

In scenario analysis, we explore the effects of including productivity/indirect costs in the model. To be clear, this is not a comprehensive analysis of indirect costs, but only focuses on lost earnings due to HCV based on the human capital method. We follow Patruni and Nolte (2013)[121], who sought to assess the healthcare and economic burden of hepatitis C virus (HCV) infection in the United Kingdom for the Hepatitis C Trust. We assume that patients with HCV who are in the labour force have diminished productivity conditional on the HCV state that they are in, per the table below.

Table 126: Productivity rate by health state applied in the model

Health state	Productivity rate
Mild	100%
Moderate	100%
CC (Chronic HCV)	80%
Recovered, no HCV, history of mild fibrosis	100%
Recovered, no HCV, history of moderate fibrosis	100%
Recovered, no HCV, history of severe fibrosis (CC)	100%
DCC	0%
HCC (first year)	0%
HCC (subsequent year)	0%
Liver transplant (first year)	80%
Liver transplant (subsequent)	80%

We multiply this diminished productivity rate by the age adjusted likelihood of being in the labour force (i.e., “economically active” per Table DC6107EW - Economic Activity by sex by age) each year. We multiply that product by age-adjusted wages (per

Table 6.7a Annual pay - Gross (£) - For all employee jobs: United Kingdom, 2013 in Annual Survey of Hours and Earnings, Office for National Statistics) and then by the likelihood of survival. This is done for each year the patient could be alive to age 80, at which point expected wages and labour force participation are expected to be zero. We create a counterfactual—an identical scenario where the patient does not have HCV, and has the same life expectancy, expected wages and labour force participation as the average person in the UK. We take the difference and consider this the indirect cost loss.

Grishchenko et al. (2009)

In the base case, we use transitional probabilities described in Shepherd et al., 2007 which were in turn sourced from the economic evaluation undertaken alongside the UK Mild hepatitis C Trial. In a scenario analysis, we also assess results using transitional probabilities from Grishchenko et al., 2009[66] who assumed different fibrosis progression rates by age at presentation for treatment (30 versus 40 versus 50 years old). For further details, please refer to section 7.3.3 of the submission.

Alternative efficacy estimates for PR

PR SVR estimates for treatment naïve patients in our model base case are based on the SVRs of patients receiving peginterferon alfa-2a and ribavirin alone (PR group) in the ADVANCE trial. We realise that this may be deemed a limitation of our submission, however PR SVR estimates in the ADVANCE study are higher than those observed in for example SPRINT-2 trial (a corresponding trial of boceprevir and peginterferon alfa-2b where observed SVR in GT1 Group 1 patients = 38%) making our assumption a conservative one. In addition, we explore this in scenario analyses where we apply SVR rates reported in McHutchinson et al., 2009[87] and Hadziyannis et al., 2004[88] studies.

Scenario analyses on health state utilities (HSUs) in the model

In scenario analysis (HSU scenario 1; Table 127), the Recovered states (i.e., SVR states) assume a 0.90/0.86 increase (an approximate 4.65% SVR related increment) in health utility over their corresponding chronic HCV state (i.e., chronic HCV state health utility X 0.90/0.86) based on Vera-Llonch et al. (2013), who assessed 72 week HRQL for HCV patients receiving telaprevir combination therapy in the ADVANCE study.[122] All other health utility values are the same as in the base case.

In another scenario analysis ("AbbVie trial"/HSU scenario 2; Table 127), it is assumed that the chronic HCV (mild, moderate and compensated cirrhosis) states are based on the AbbVie Regimen baseline trial UK Crosswalk EQ-5D observations (see section 7.4 for more information). Further, instead of the +0.05 increment being applied uniformly to the baseline utilities of all treated patients who achieve SVR, the increment associated with the Recovered health states for all therapies is now based on the annualised difference in health utility between the baseline and post-treatment week 12 utility values from the AbbVie Regimen trials. Patient segments are stratified by fibrosis severity (mild, moderate, compensated cirrhosis), genotype and treatment experience (naïve, null, partial, prior relapse). In other words, for those reaching SVR, there is no possibility for a greater increase in health utility than what was observed in the trials at post-treatment week 12. It is worth noting that during PTW12 visit when the EQ-5D questionnaire was filled in, the majority of patients were uninformed of their SVR status. It is therefore plausible that post-treatment QoL gains may have been underestimated.

In the PEARL I trial of genotype 4 patients without cirrhosis, post-treatment week 12 EQ-5D data was not collected; in place, we use post-treatment week 24 data for this group of patients. Moreover, in treatment-experienced GT4 patients, post-treatment week 24 data was not yet available at the time of submission; we thus impute the week 24 utility data by extrapolating the difference between PTW24 and baseline EQ-5D for treatment-naïve GT4 patients onto the baseline utility observed for the GT4 treatment-experienced patients. To derive utilities for the HCC, DCC and liver transplant health states, we apply the decrement (utility difference) between the mild and the HCC, DCC and liver transplant health states observed in Wright et al. (2006) to the mild health state utility observed in the AbbVie Regimen trials.

Table 127 below details the base case input values for health utilities together with the two scenario analyses described above.

Table 127: Health state utilities: base case and scenario analyses

Parameter	Base case	HSU scenario 1	HSU scenario 2
Health Utilities			
Mild	0.770	0.770	[redacted]
Moderate	0.660	0.660	[redacted]
CC (Chronic HCV)	0.550	0.550	[redacted]
Recovered, no HCV, history of mild fibrosis	0.820	0.806	[redacted]
Recovered, no HCV, history of moderate fibrosis	0.710	0.691	[redacted]
Recovered, no HCV, history of severe fibrosis (CC)	0.600	0.576	[redacted]
DCC	0.450	0.450	[redacted]
HCC (first year)	0.450	0.450	[redacted]
HCC (subsequent year)	0.450	0.450	[redacted]
Liver transplant (first year)	0.450	0.450	[redacted]
Liver transplant (subsequent)	0.670	0.670	[redacted]

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Non-treatment-specific and treatment-specific variables related to health state costs, utilities and transition probabilities

DSA was performed by means of one-way and multivariate sensitivity analysis, where one variable or group of related variables was varied relative to its base case value. The non-treatment-specific and treatment-specific variables tested in DSA are shown in Table 128 below.

Table 128: Variables subject to deterministic sensitivity analysis

Parameter	Value in DSA	Value in Base-case Analysis
Progression Rates/Transitional Probabilities		
1. Mild to moderate (Shepherd)	0.013-0.037	0.025
2. Moderate to CC (Shepherd)	0.016-0.058	0.037
3. Recovered, no HCV, History of Severe Fibrosis (CC) to HCC	0.0028-0.0218	0.0123
4. CC to DCC	0.029-0.049	0.039
5. CC to HCC (First Year)	0.004-0.024	0.014
6. DCC to HCC (First Year)	0.004-0.024	0.014
7. DCC to Liver Transplant (First Year)	0.016-0.024	0.02
8. HCC to Liver Transplant (First Year)	0.016-0.024	0.02
9. DCC to Liver Death	0.12-0.14	0.13
10. Liver Transplant to Liver Death	0.12-0.18	0.15
11. After Liver Transplant to Liver Death	0.046-0.068	0.057
12. HCC First Year to Liver Death	0.40-0.46	0.43
13. HCC Subsequent Year to Liver Death	0.40-0.46	0.43
14. Viral Reinfection	0.00-0.02	0.01
Direct Medical Costs		
15. Mild	Direct medical costs are varied using +/- 50% of base values except when confidence interval is provided in Backx (i.e., Moderate, CC, and all three recovered states)	£160
16. Moderate		£589
17. CC (Chronic HCV)		£914
18. Recovered, no HCV, history of mild fibrosis		£58
19. Recovered, no HCV, history of moderate fibrosis		£58
20. Recovered, no HCV, history of severe fibrosis (CC)		£586
21. DCC		£12,333
22. HCC (first year)		£10,990
23. HCC (subsequent year)		£10,990
24. Liver transplant (first year)		£49,749
25. Liver transplant (subsequent)		£1,873
Health Utilities		
31. Mild	Health utilities are varied using +/- 20% of base values.	0.770
32. Moderate		0.660
33. CC (Chronic HCV)		0.550
34. Recovered, no HCV, history of mild fibrosis		0.820
35. Recovered, no HCV, history of moderate fibrosis		0.710
36. Recovered, no HCV, history of severe fibrosis (CC)		0.600
37. DCC		0.450
38. HCC (first year)		0.450
39. HCC (subsequent year)		0.450
40. Liver transplant (first year)		0.450
41. Liver transplant (subsequent)		0.670
Treatment-related Attributes (Intervention and Comparator varied simultaneously)		
42. SVRs in non-cirrhotics	SVRs and AEs are varied using +/- 1.96 SD of base values. Monitoring costs are varied +/- 50% of base	Values are dependent on: Patient Segment Patient Genotype Intervention
43. SVRs in cirrhotics		
44. Rate of Anemia		
45. Rate of Rash		
46. Rate of Depression		
47. Rate of Neutropenia		

48. Rate of Thrombocytopenia	values.	Comparator
49. Treatment-monitoring Costs		
Treatment-related Costs		
26. Anemia	Costs of AEs are varied using +/- 50% of base values.	£482
27. Rash		£160
28. Depression		£398
29. Neutropenia		£942
30. Thrombocytopenia		£841

Treatment-related attributes (i.e. SVR, AE rates, and monitoring costs) are dependent on patient segment (e.g., genotype, treatment-history), and were each varied simultaneously for the intervention and comparator. For instance, each AE of the intervention and comparator are varied simultaneously. SVRs and AE rates derived directly from the clinical trials were described in section 7.3. It is worth highlighting that there were patient segments in which the observed SVR rate was 100% or the observed AEs were 0% (see section 7.3.1). In order to generate CIs in such instances, we use method advocated by Briggs et al. (2003) to infer that for example the observed 100% SVR rates are imprecisely measured (in a sense that a patient could fail to have an SVR, though improbably) and that the rates have uncertainty around them.[123] To impute the uncertainty, we assume a conservative prior distribution for regimen SVRs by patient segment in the analysis, assuming that the first patient observation is a failure (numerator 0, denominator 1, SVR = 0%). Then we effectively add the observations from the trials into the model and compute standard errors assuming they take on a binomial distribution. Equally, to impute uncertainty into the AEs measurement (where the observed AEs were 0%), we assume that the prior distribution is based on one patient who had an AE.

Monitoring costs are varied +/-50% base case values. Treatment history, genotype, background death rate and regimen prices were not varied in the DSA. Treatment history and genotype define patient segments. Background death rate is based on large national samples with little measurement error.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was undertaken in the analysis in all patient segments (naïve, null responder, partial responder prior relapse, IFN-unsuitable, and naïve GT4) for each indicated comparator and the AbbVie Regimen. Table Table 129 contains the list of model parameters with associated sampling uncertainty included in the PSA as well as statistical moments used and the parametric distribution assumed for each variable. Given that multiple treatment options were available in segments, we used a cost-effectiveness acceptability frontier (CEAF) approach, monetizing QALYs to employ a net monetary benefits (NMB) framework. For each CEAF, 500 simulations were drawn from the variables' assumed distributions. SVR and AE rates derived directly from the clinical trials (and applying the method of Briggs et al. [2003]) were assumed

to have a beta distribution that are characterized by the trial segment sample size and percentage with SVR and AE respectively; we impute the lower (upper) bound for SVR (AE) as described in the DSA (see Section 7.6.2). Variables excluded from the PSA included those excluded from the DSA, with the addition of some late-stage transitions (identified in the table below, for example the transitional probability from DCC to liver transplant, derived from Hartwell et al. (2011), who did not indicate PSA parameters for these variables.

Table 129: Variables included in the PSA

Variable	Base Case Value	Sensitivity, Low	Sensitivity, High	PSA, Second Statistical Moment[§]	Distribution in PSA
Transition probabilities (annual)					
Fibrosis progression					
Shepherd et al. (base case)					
Mild to moderate	0.025	0.013	0.037	0.004	Beta
Moderate to CC	0.037	0.016	0.058	0.007	Beta
Non-fibrosis progression					
Recovered, no HCV, history of severe fibrosis (CC) to HCC	0.012	0.003	0.022	0.011	Beta
CC to DCC	0.039	0.029	0.049	0.010	Beta
CC to HCC (first year)	0.014	0.004	0.024	0.010	Beta
DCC to HCC (first year)	0.014	0.004	0.024	0.010	Beta
Liver-related mortality					
DCC to liver death	0.130	0.120	0.140	0.010	Beta
Liver transplant to liver death	0.150	0.000	0.000	None	None
After liver transplant to liver death	0.057	0.000	0.000	None	None
HCC first year to liver death	0.430	0.400	0.460	0.030	Beta
HCC subsequent year to liver death	0.430	0.400	0.460	0.0300	Beta
Viral re-infection	0.010	0.000	0.020	0.010	Beta
Costs (annual)					
Direct medical costs by health state					
Mild	£160	£80[^]	£240[^]	£160	Gamma
Moderate	£589	£417[^^]	£833[^^]	£589	Gamma
CC (chronic HCV)	£914	£560[^^]	£1,491[^^]	£914	Gamma
Recovered, no HCV, history of mild fibrosis	£58	£45[^^]	£75[^^]	£58	Gamma

Variable	Base Case Value	Sensitivity, Low	Sensitivity, High	PSA, Second Statistical Moment[§]	Distribution in PSA
Recovered, no HCV, history of moderate fibrosis	£58	£45[^^]	£75[^^]	£58	Gamma
Recovered, no HCV, history of severe fibrosis (CC)	£586	£207[^^]	£1,655[^^]	£586	Gamma
DCC	£12,333	£6,167[^]	£18,500[^]	£12,333	Gamma
HCC (first year)	£10,990	£5,495[^]	£16,485[^]	£10,990	Gamma
HCC (subsequent year)	£10,990	£5,495[^]	£16,485[^]	£10,990	Gamma
Liver transplant (first year)	£49,749	£24,875[^]	£74,624[^]	£49,749	Gamma
Liver transplant (subsequent)	£1,873	£937[^]	£2,810[^]	£1,873	Gamma
Monitoring costs					
AbbVie Regimen					
12 weeks	£468.03	£234.01[^]	£702.04[^]	None	None
24 weeks	£936.06	£468.03[^]	£1,404.09[^]	None	None
SOF + PR/12 weeks	£468.03	£234.01[^]	£702.04[^]	None	None
TPR or BOC + PR/24 weeks	£936.06	£457.94[^]	£1,373.81[^]	None	None
TPR or BOC + PR/28 weeks	£915.87	£495.88[^]	£1,487.65[^]	None	None
TPR or BOC + PR/36 weeks	£991.77	£573.83[^]	£1,721.49[^]	None	None
TPR or BOC + PR/48 weeks	£1,147.66	£692.27[^]	£2,076.81[^]	None	None
Treatment-related adverse event costs					
Anaemia	£482	£241[^]	£723[^]	£482	Gamma
Rash	£160	£80[^]	£240[^]	£160	Gamma
Depression	£398	£199[^]	£596[^]	£398	Gamma
Neutropenia	£942	£471[^]	£1,413[^]	£942	Gamma
Thrombocytopenia	£841	£421[^]	£1,262[^]	£841	Gamma
Health state utilities [Ψ]					
Mild	0.770	0.616**	0.924**	0.031	Beta

Variable	Base Case Value	Sensitivity, Low	Sensitivity, High	PSA, Second Statistical Moment[§]	Distribution in PSA
Moderate	0.660	-0.180**	-0.040**	0.070	Log-normal
CC (chronic HCV)	0.550	-0.300**	-0.130**	0.085	Log-normal
Recovered, no HCV, history of mild fibrosis	0.820	0.656**	0.984**	Assumed to be perfectly correlated with Mild state (+0.05)	None
Recovered, no HCV, history of moderate fibrosis	0.710	0.568**	0.852**	Assumed to be perfectly correlated with Moderate state (+0.05)	None
Recovered, no HCV, history of severe fibrosis (CC)	0.600	0.480**	0.720**	Assumed to be perfectly correlated with CC state (+0.05)	None
DCC	0.450	0.360**	0.540**	0.090[Θ]	Beta
HCC (first year)	0.450	0.360**	0.540**	0.090[Θ]	Beta
HCC (subsequent year)	0.450	0.360**	0.540**	0.090[Θ]	Beta
Liver transplant (first year)	0.450	0.536**	0.804**	0.134[Θ]	Beta
Liver transplant (subsequent)	0.670	0.536**	0.804**	0.134[Θ]	Beta

CC = compensated cirrhosis; HCC = hepatocellular carcinoma; DCC = decompensated cirrhosis; PSA = probabilistic sensitivity analysis.
[§] Second statistical moment is standard error where available. If standard error was not available, standard deviation was used. If neither were available for a beta distribution, the N was used and a binomial distribution was assumed.
[^] Univariate sensitivity analysis bounds assumed to be +/-50% of base case.
[^^] Univariate sensitivity analysis bounds are taken from Backx et al. (2014).
** Univariate sensitivity analysis bounds assumed to be +/-20% of base case.
[Ψ] Additional scenario analyses were undertaken, as described in section 7.6.1.
[Θ] Standard error assumed to be one-half the average absolute difference in mean and upper and lower bound

7.7 Results

Clinical outcomes from the model

7.7.1 **For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.**

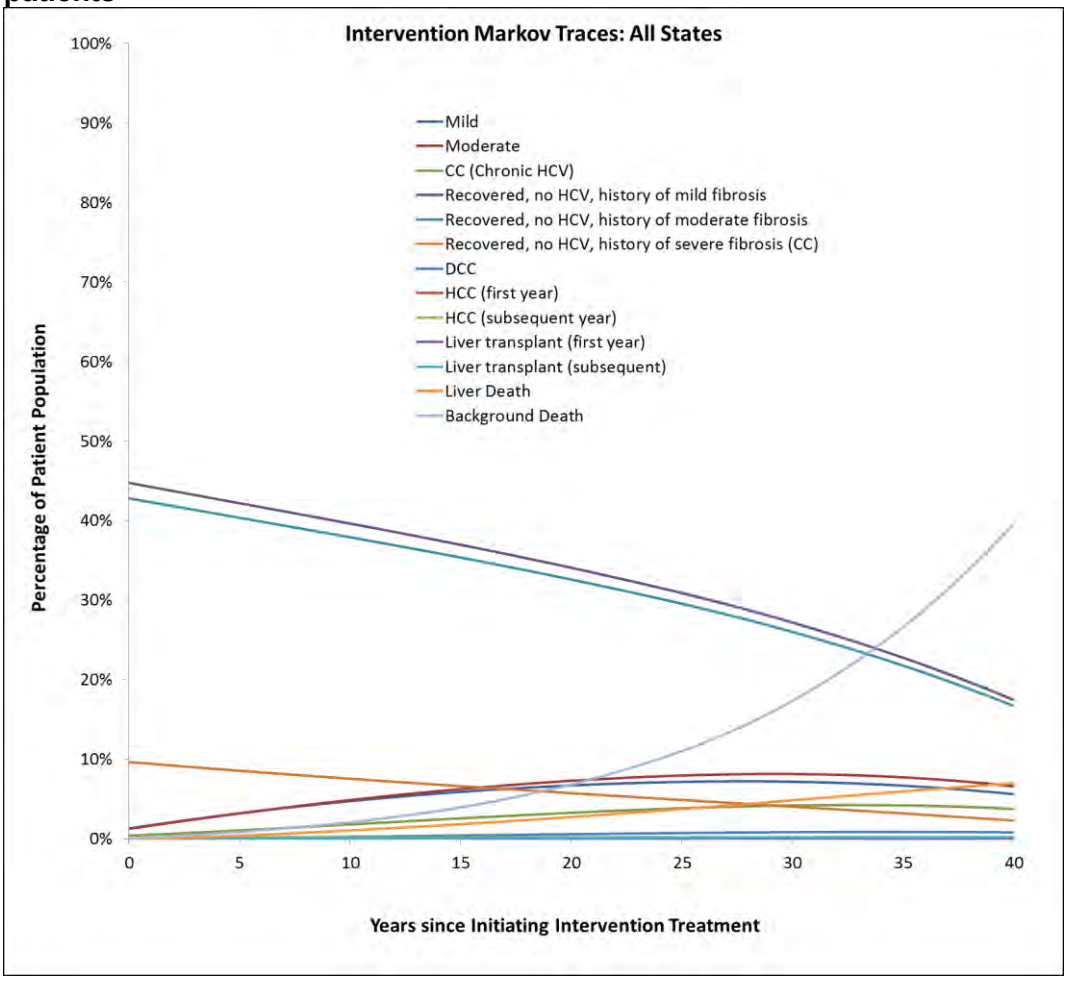
In the base case, the main clinical outcome modelled for each treatment, namely the proportion (%) of patients achieving SVR, were obtained from observed clinical trials outcome analysis data and identical to the clinical trials data. A detailed description of the SVR outcomes applied in the model was provided in Section 7.3 of the submission.

7.7.2 **Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.**

Markov traces for patients treated with the AbbVie Regimen (intervention) who are GT1 naïve is presented in the Figure 27 below showing the distribution (%) of the patient cohort across model health states over time. Markov traces for each relevant treatment and patient subgroup (genotype, treatment experience) combination are available upon request.

Markov Traces

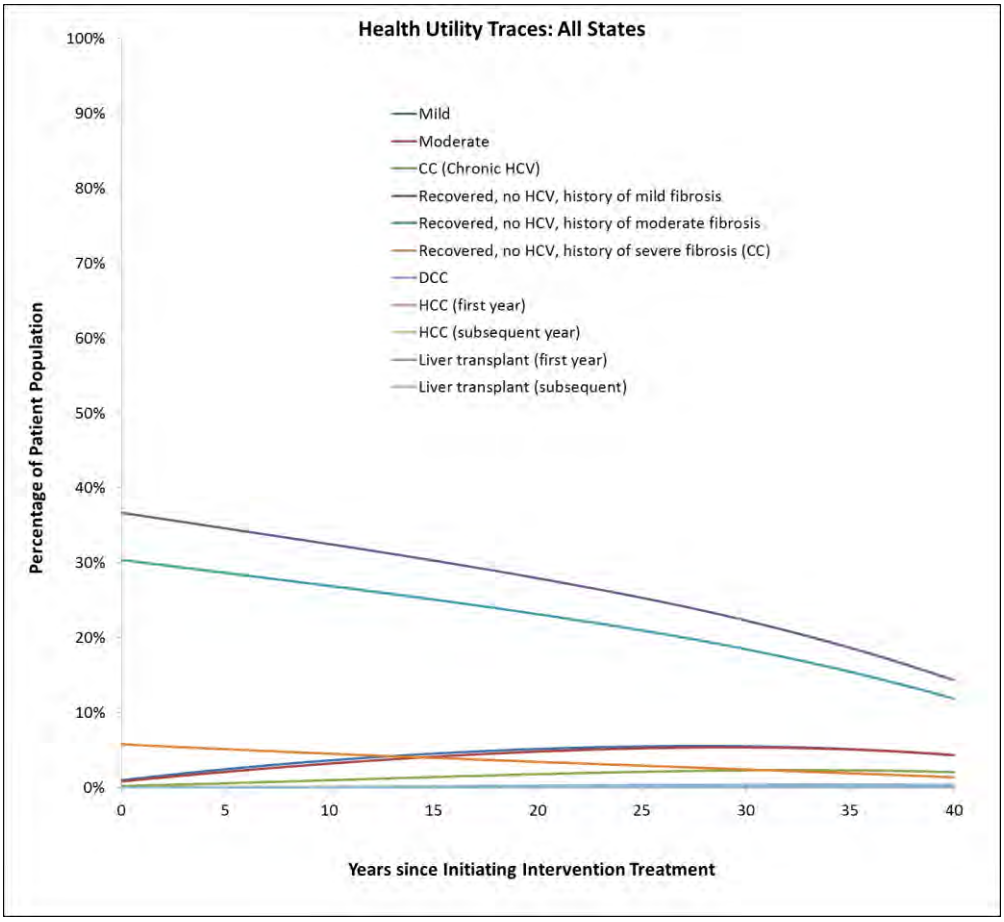
Figure 27: AbbVie Regimen Markov traces in GT1, treatment-naïve (IFN-eligible) patients



7.7.3 **Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.**

QALYs in each 1-year cycle are accrued by multiplying the number of patients in each health state by the utility for that state and applying discount (3.5% per year in base case). To calculate the ICER, QALYs are then summed across the time horizon of the analysis (lifetime in base case). The trace for GT1, treatment-naïve patients receiving the AbbVie Regimen appears in Figure 28 below. Patient Markov traces showing QALYs accrued by the patient cohort in each health state over time, one for each relevant treatment and patient subgroup (genotype, treatment history) combination, are available upon request.

Figure 28: AbbVie Regimen QALY traces in GT1, treatment-naïve (IFN-eligible) patients



7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Model outputs by clinical outcome and total costs for GT1 and GT4, INF-eligible, treatment naïve and treatment experienced patients are presented in the tables below for each relevant therapy. Costs, LYs, and QALYs have been discounted at a rate of 3.5% per year over a lifetime horizon.

Across both genotypes and patient populations, although the total discounted cost per patient treated with the AbbVie Regimen is higher than with most comparators, it is associated with significant improvements in health outcomes, including reductions in long-term complications such as DCC, HCC, liver transplant, and liver-related mortality.

Table 130: Model outputs by clinical outcomes for GT1, treatment-naïve (IFN-eligible) patients

Outcome	Cost (£)/patient	QALYs/ patient	LYs/ patient	Percentage ever reaching CC	Percentage ever reaching DCC	Percentage ever reaching HCC	Percentage ever reaching Liver Transplant	Percentage ever having a liver-related death
AbbVie Regimen	£43,624	15.21	20.59	20.9%	5.6%	5.4%	0.7%	8.7%
Sofosbuvir + PR	£44,337	15.01	20.46	23.1%	7.4%	5.7%	1.0%	10.4%
Telaprevir + PR	£35,887	14.55	20.16	29.6%	11.7%	7.0%	1.5%	14.8%
PR	£22,872	13.72	19.68	41.5%	18.9%	9.2%	2.3%	22.2%
Boceprevir + PR	£32,147	14.22	19.94	33.1%	14.9%	7.4%	1.8%	17.6%

Table 131: Model outputs by clinical outcomes for GT1, treatment-experienced (IFN-eligible, overall) patients

Outcome	Cost (£)/patient	QALYs/patient	LYs/patient	Percentage ever reaching CC	Percentage ever reaching DCC	Percentage ever reaching HCC	Percentage ever reaching Liver Transplant	Percentage ever having a liver-related death
AbbVie Regimen	£51,882	13.19	18.72	39.0%	6.4%	11.8%	1.1%	15.2%
Sofosbuvir + PR	TBD	TBD	TBD	TBD	TBD	TBD	TBD	TBD
Telaprevir + PR	£42,646	12.10	17.92	47.9%	18.1%	12.4%	2.4%	24.8%
PR	£30,128	11.07	17.13	61.7%	29.9%	14.3%	3.7%	35.5%
Boceprevir + PR	TBD	TBD	TBD	TBD	TBD	TBD	TBD	TBD

TBD, to be determined because cannot be assessed with current available data.

Table 132: Model outputs by clinical outcomes for GT4, treatment-naïve non-cirrhotic patients

Outcome	Cost (£)/patient	QALYs/patient	LYs/patient	Percentage ever reaching CC	Percentage ever reaching DCC	Percentage ever reaching HCC	Percentage ever reaching Liver Transplant	Percentage ever having a liver-related death
AbbVie Regimen	£36,490	15.84	20.98	10.9%	4.0%	1.7%	0.4%	3.9%
SOF + PR	£41,237	15.81	20.98	10.9%	4.0%	1.7%	0.4%	3.9%
PR	£19,286	15.00	20.58	23.6%	10.3%	4.4%	1.2%	10.9%

Table 133: Model outputs by clinical outcomes for GT4, treatment-experienced non-cirrhotic patients

Outcome	Cost (£)/patient	QALYs/patient	LYs/patient	Percentage ever reaching CC	Percentage ever reaching DCC	Percentage ever reaching HCC	Percentage ever reaching Liver Transplant	Percentage ever having a liver-related death
AbbVie Regimen	£36,536	14.84	19.71	9.2%	3.2%	1.3%	0.3%	3.0%
No Treatment	£16,186	12.58	18.57	50.4%	22.3%	9.5%	2.5%	23.7%

7.7.5 **Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.**

The disaggregated incremental QALYs and costs by health state and predicted resource use are shown below for the GT1, IFN-eligible, treatment-naïve patients: AbbVie Regimen vs. SOF + PR comparison. Other comparisons for each genotype and treatment history are available upon request.

Table 134: Summary of QALY gain by health state in GT1, treatment-naïve (IFN-eligible) patients: AbbVie Regimen vs. SOF + PR (undiscounted)

Health state	QALYs/patient intervention (AbbVie Regimen)	QALYs/patient comparator (SOF + PR)	Increment	Absolute increment	% absolute increment
Treatment-related health utility	0.00	-0.03	0.03	0.03	7%
Mild	2.10	2.48	-0.38	0.38	86%
Moderate	2.01	2.39	-0.38	0.38	87%
CC	0.82	1.08	-0.26	0.26	59%
Recovered, history of mild	11.99	11.30	0.69	0.69	155%
Recovered, history of moderate	9.93	9.36	0.57	0.57	129%
Recovered, history of CC	1.49	1.25	0.24	0.24	55%
DCC	0.12	0.17	-0.05	0.05	10%
HCC	0.05	0.06	0.00	0.00	1%
Liver transplant	0.04	0.06	-0.01	0.01	3%
Total	**28.56**	**28.11**			

CC = compensated cirrhosis; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; QALY = quality-adjusted life-year.

Table 135: Summary of costs by health state in GT1, treatment-naïve (IFN-eligible) patients: AbbVie Regimen vs. SOF + PR (undiscounted)

Health state	Cost/patient intervention (AbbVie Regimen)	Cost/patient comparator (Sofosbuvir + PR)	Increment	Absolute increment	% absolute increment
Mild	£437	£516	-£78	£78	4%
Moderate	£1,795	£2,136	-£341	£341	17%
CC	£1,359	£1,793	-£434	£434	22%
Recovered, history of mild	£848	£799	£49	£49	2%
Recovered, history of	£811	£765	£46	£46	2%

moderate					
Recovered, history of CC	£1,456	£1,221	£235	£235	12%
DCC	£3,374	£4,632	-£1,258	£1,258	63%
HCC	£1,280	£1,354	-£74	£74	4%
Liver transplant	£478	£620	-£142	£142	7%
Total	**£11,839**	**£13,836**			

CC = compensated cirrhosis; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma.

Table 136: Summary of predicted resource use by category of cost in GT1, treatment-naïve (IFN-eligible) patients: AbbVie Regimen vs. SOF + PR (undiscounted)

Item	Cost/patient intervention (AbbVie Regimen)	Cost/patient comparator (SOF + PR)	Increment	Absolute increment	% absolute increment
DAA	£37,078	£34,606	£2,472	£2,472	704%
PR	£692	£2,528	-£1,835	£1,835	523%
Treatment-related AE	£41	£360	-£318	£318	91%
Treatment Monitoring Costs	£500	£468	£32	£32	9%
Total	£38,312	£37,961			

AE = adverse event.

Base-case analysis

7.7.6 **Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.**

Base case cost-effectiveness results are presented below separately for genotype-1 and genotype 4, treatment naïve and treatment experienced interferon eligible patients.

Table 137 and Table 138 show the incremental cost-effectiveness results for AbbVie 3D regimen, BOC+PR, TPR+PR and SOF+PR versus PR in GT1, treatment naïve (Table 137) and treatment experienced (overall), interferon eligible patients (Table 138) respectively.

Table 139 details the results of the incremental cost-effectiveness analysis for AbbVie 2D regimen and SOF+PR over PR in GT4, treatment-naïve, interferon-eligible patients, whereas Table 140 shows results for GT4, treatment-experienced patients.

The ICERs were also calculated between the AbbVie Regimen and each comparator in a pairwise comparison in each patient segment. A summary Table 141 is presented below.

Genotype 1 patients

Table 137: Base-case results for GT1, treatment-naïve, interferon eligible patients

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£22,872	19.68	13.72	NA	NA	NA	NA	NA
Boceprevir + PR	£32,147	19.94	14.22	£9,275	0.26	0.50	£18,366	Extended dominance
Telaprevir + PR	£35,887	20.16	14.55	£13,014	0.48	0.83	£15,602	Extended dominance
AbbVie Regimen	£43,624	20.59	15.21	£20,752	0.91	1.50	£13,864	£13,864
Sofosbuvir + PR	£44,337	20.46	15.01	£21,465	0.78	1.29	£16,618	Dominated

Table 138: Base-case results for GT1, treatment-experienced (overall) interferon eligible patients

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£30,128	17.13	11.07	NA	NA	NA	NA	NA
Telaprevir + PR	£42,646	17.92	12.10	£12,518	0.78	1.04	£12,095	Extended dominance
AbbVie Regimen	£51,882	18.72	13.19	£21,754	1.58	2.12	£10,258	£10,258

Genotype 4 patients

Table 139: GT4, treatment-naïve, interferon-eligible patients (non-cirrhotic only)

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£19,286	20.58	15.00	NA	NA	NA	NA	NA
AbbVie Regimen	£36,490	20.98	15.84	£17,204	0.40	0.85	£20,351	£20,351

Sofosbuvir + PR	£41,237	20.98	15.81	£21,951	0.40	0.81	£27,135	Dominated

Table 140: GT4, treatment-experienced (overall) interferon eligible patients (non-cirrhotic only)

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. NT	ICER incremental
No treatment	£16,186	18.57	12.58	NA	NA	NA	NA	NA
AbbVie Regimen	£36,536	19.71	14.84	£20,350	1.14	2.27	£8,977	£8,977

NT: No treatment

Table 141: Summary of cost-effectiveness results for AbbVie Regimen versus each comparator: £/QALY

	AbbVie Regimen versus SOF + PR	AbbVie Regimen versus TPR + PR	AbbVie Regimen versus PR	AbbVie Regimen versus BOC + PR	AbbVie Regimen versus No Treatment
Naïve GT1, IFN eligible	Dominant	£11,677	£13,864	£11,572	NA
Treatment Experienced (Overall) GT1	TBD	£8,507	£10,258	TBD	NA
GT4, Naïve Patients, non-cirrhotic	Dominant	NA	£20,351	NA	NA
GT4, Treatment Experienced Patients non-cirrhotic	NA	NA	NA	NA	£8,977

NA, not applicable; TBD, to be determined because cannot be assessed with current available data

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Deterministic sensitivity analysis (DSA) was performed by means of one-way and multivariate sensitivity analysis, where one parameter or group of related parameters were varied relative to its base case value. The method adopted and the parameters tested were described in section 7.6.2.

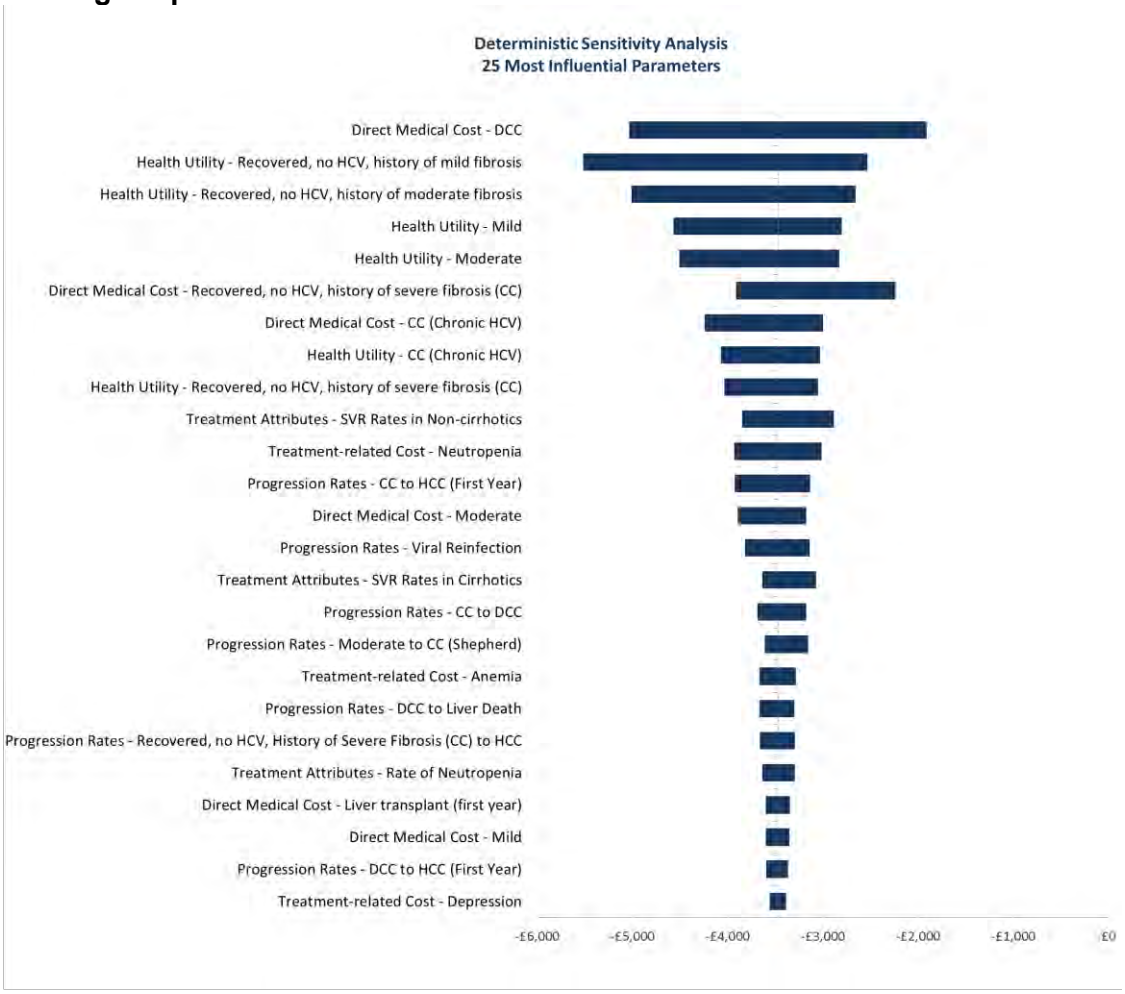
The impact of variation in treatment efficacy (SVR), adverse event rates, costs, utilities, and transition probabilities were tested in sensitivity analysis. The size of the impact (i.e., change in the ICER from the base case) was then ranked and the 25 most influential disease model parameters and treatment attributes are listed below for each intervention/comparator comparison in the GT1 and GT4, IFN-eligible chronic HCV patients. Tornado diagrams in GT1 and GT4, IFN-unsuitable patients are available upon request.

GT1, treatment-naïve, IFN-eligible patients

AbbVie Regimen vs. SOF + PR

The base case analysis shows the AbbVie Regimen to be 'dominant' vs. SOF + PR in GT1 treatment naïve IFN-eligible patients (i.e., associated with lower costs and higher QALYs). The tornado diagram is shown in the figure below. Costs of DCC, health utility for the recovered, history of mild HCV state, and health utility for the recovered, history of moderate HCV state have the greatest impact on the results, but the AbbVie Regimen remains 'dominant' in all scenarios.

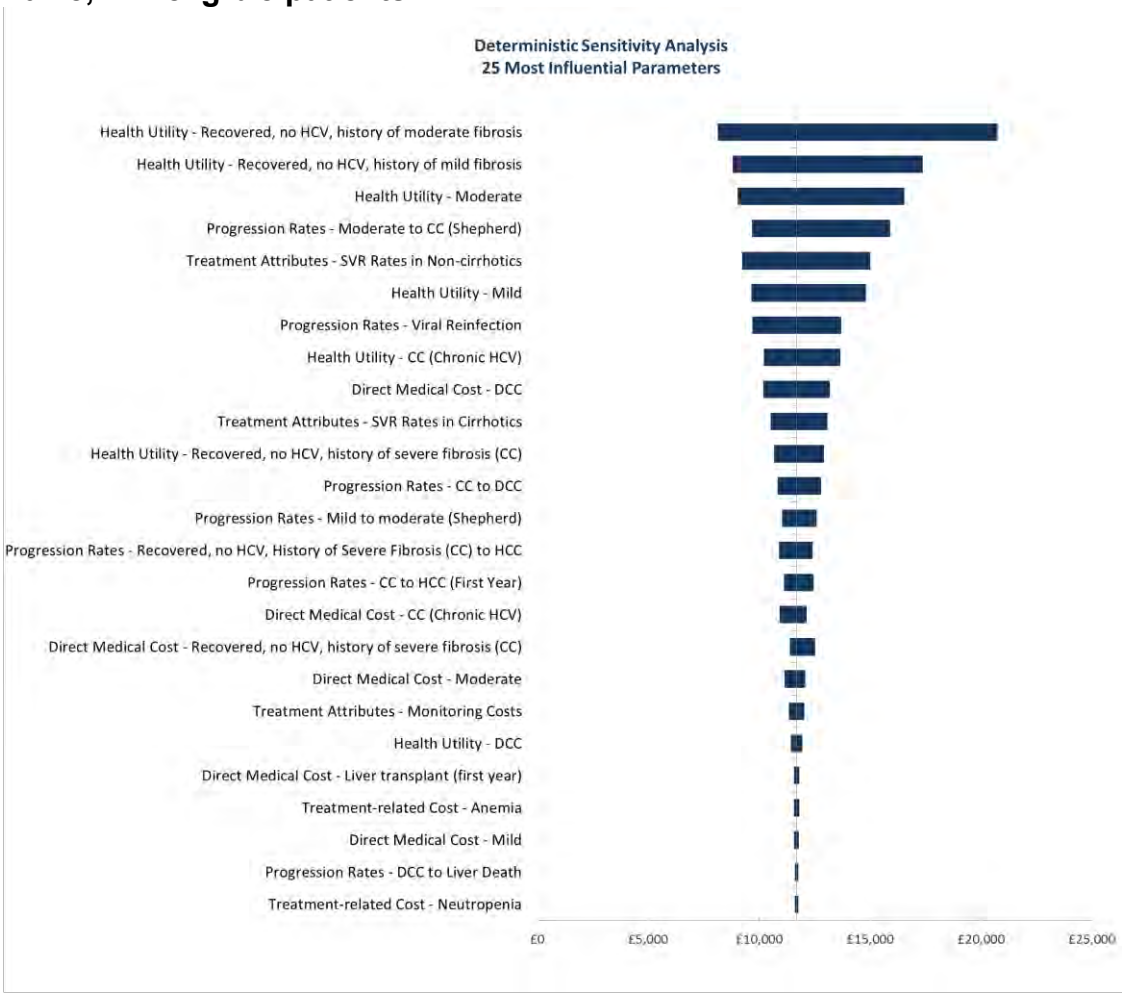
Figure 29: DSA AbbVie Regimen (3D) versus SOF + PR in GT1, treatment-naive, IFN-eligible patients



AbbVie Regimen vs. TPR + PR

The base case ICER for 3D compared with TPR + PR in GT1, treatment-naive, IFN-eligible patients is £11,677/QALY. The tornado diagram is shown in the figure below. Health utility for the recovered, history of moderate HCV state, and health utility for the recovered, history of mild HCV state, and health utility of the moderate state have the greatest impact on the results. The AbbVie Regimen has an ICER below £30,000/QALY in each analysis.

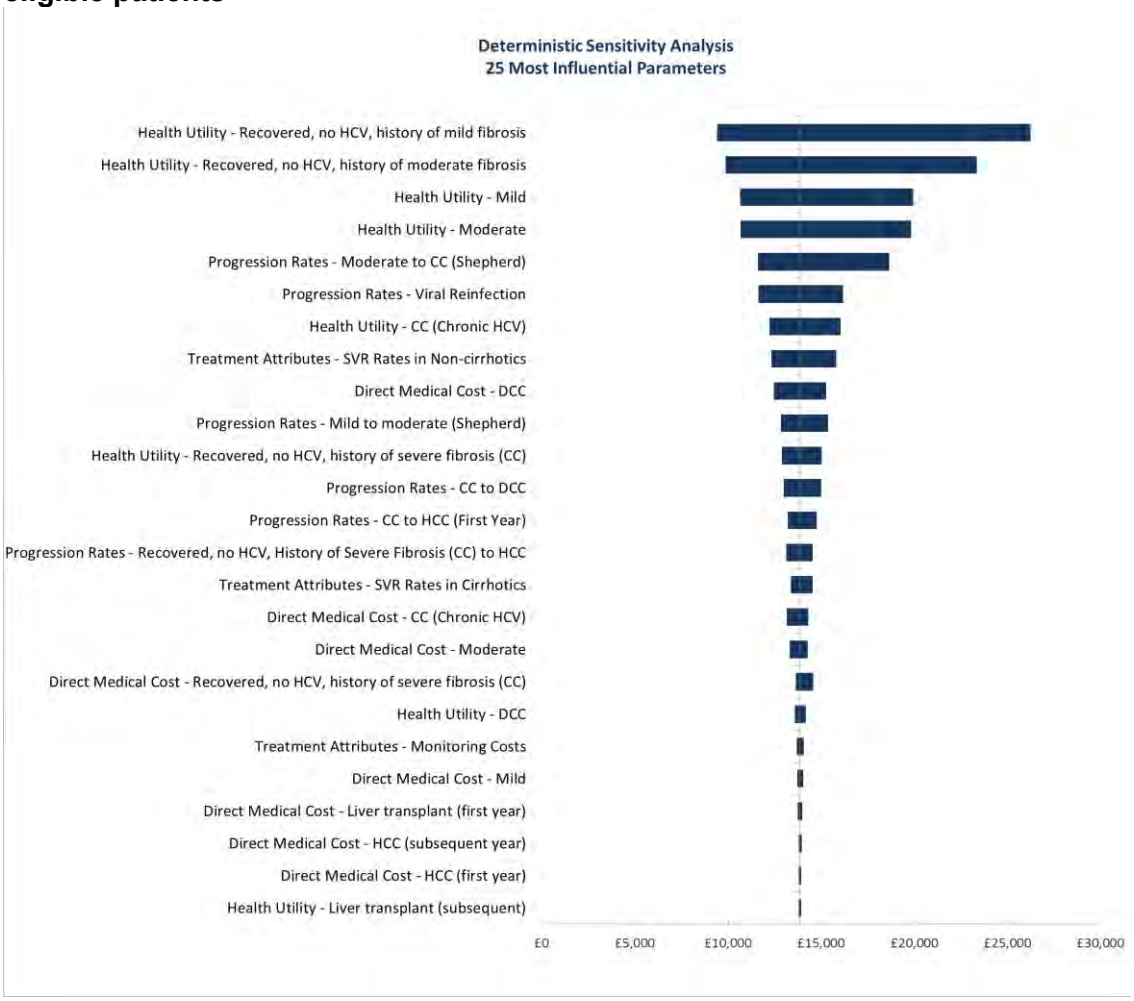
Figure 30: DSA AbbVie Regimen (3D) versus TPR + PR in GT1, treatment-naive, IFN-eligible patients



AbbVie Regimen versus PR

The base case ICER for 3D compared with PR GT1, treatment-naive, IFN-eligible patients is £13,864/QALY. The tornado diagram is shown in the figure below. Health utility for the recovered, history of moderate HCV state, and health utility for the recovered, history of mild HCV state, and health utility of the mild state have the greatest impact on the results. The AbbVie Regimen has an ICER below £30,000/QALY in each analysis.

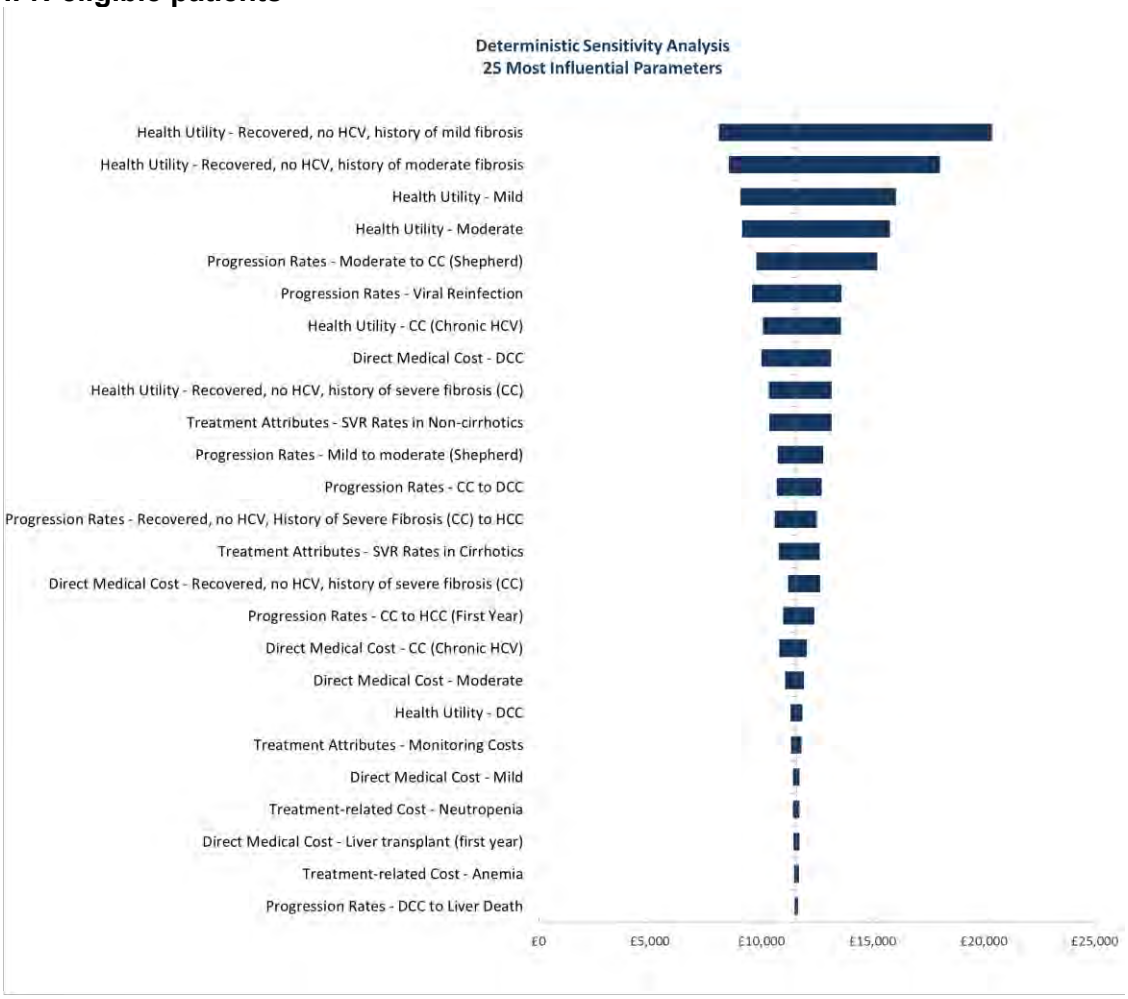
Figure 31: DSA AbbVie Regimen (3D) versus PR in GT1, treatment-naive, IFN-eligible patients



AbbVie Regimen vs. BOC + PR

The base case ICER for 3D compared with BOC + PR in GT1, treatment-naive, IFN-eligible patients is £11,572/QALY. The tornado diagram is shown in the figure below. Health utility for the recovered, history of moderate HCV state, and health utility for the recovered, history of mild HCV state, and health utility of the mild state have the greatest impact on the results. The AbbVie Regimen has an ICER below £30,000/QALY in each analysis.

Figure 32: DSA AbbVie Regimen (3D) versus BOC+ PR in GT1, treatment-naive, IFN-eligible patients

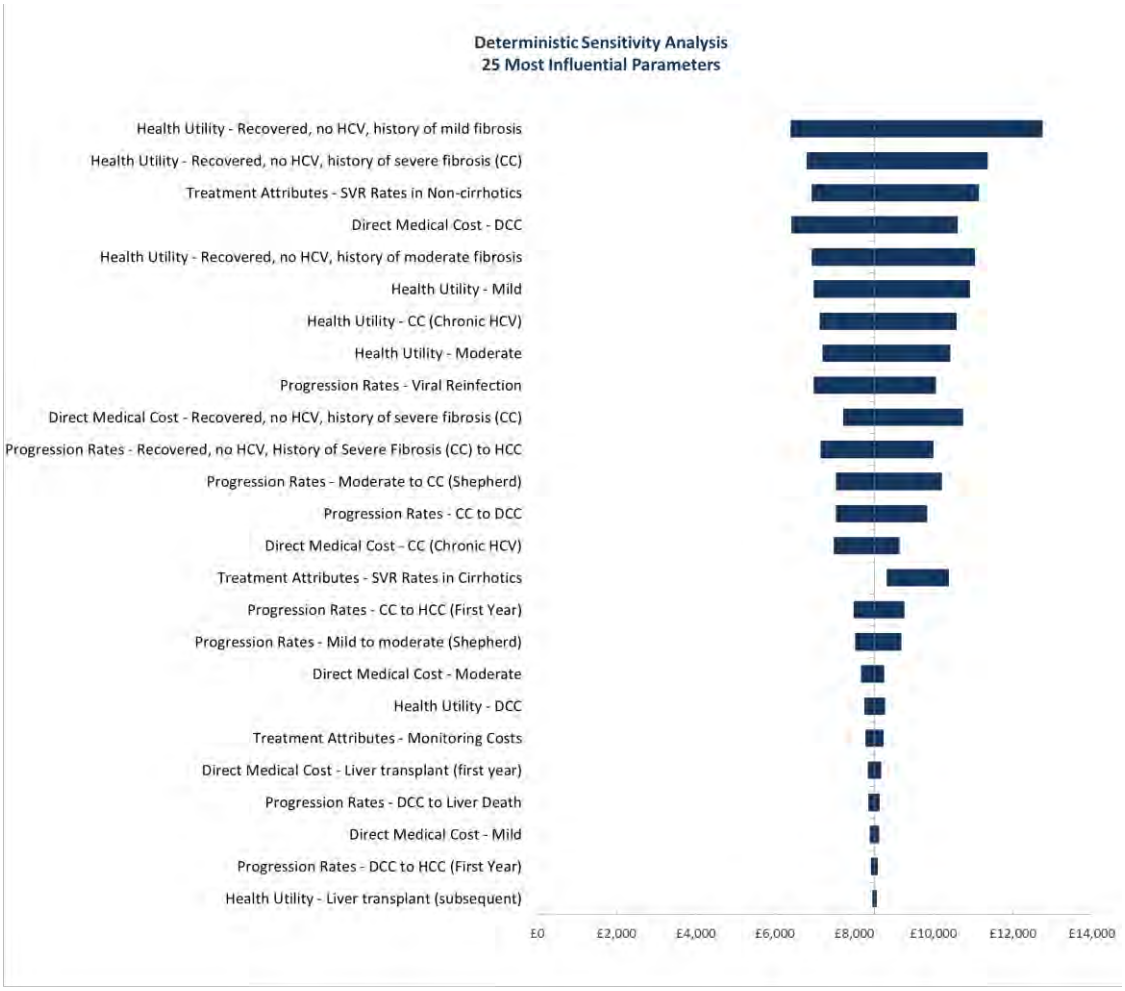


GT1, Treatment-experienced (Overall), IFN-eligible Patients

AbbVie Regimen versus TPR + PR

The base case ICER for AbbVie Regimen compared with BOC + PR is £8,507/QALY. The tornado diagram is shown in the figure below. Health utility for the recovered, history of mild fibrosis, health utility for the recovered, history of severe fibrosis (CC), and SVR rate in non-cirrhotics have the greatest impact on the results. However, the AbbVie Regimen has an ICER below £30,000/QALY in each analysis.

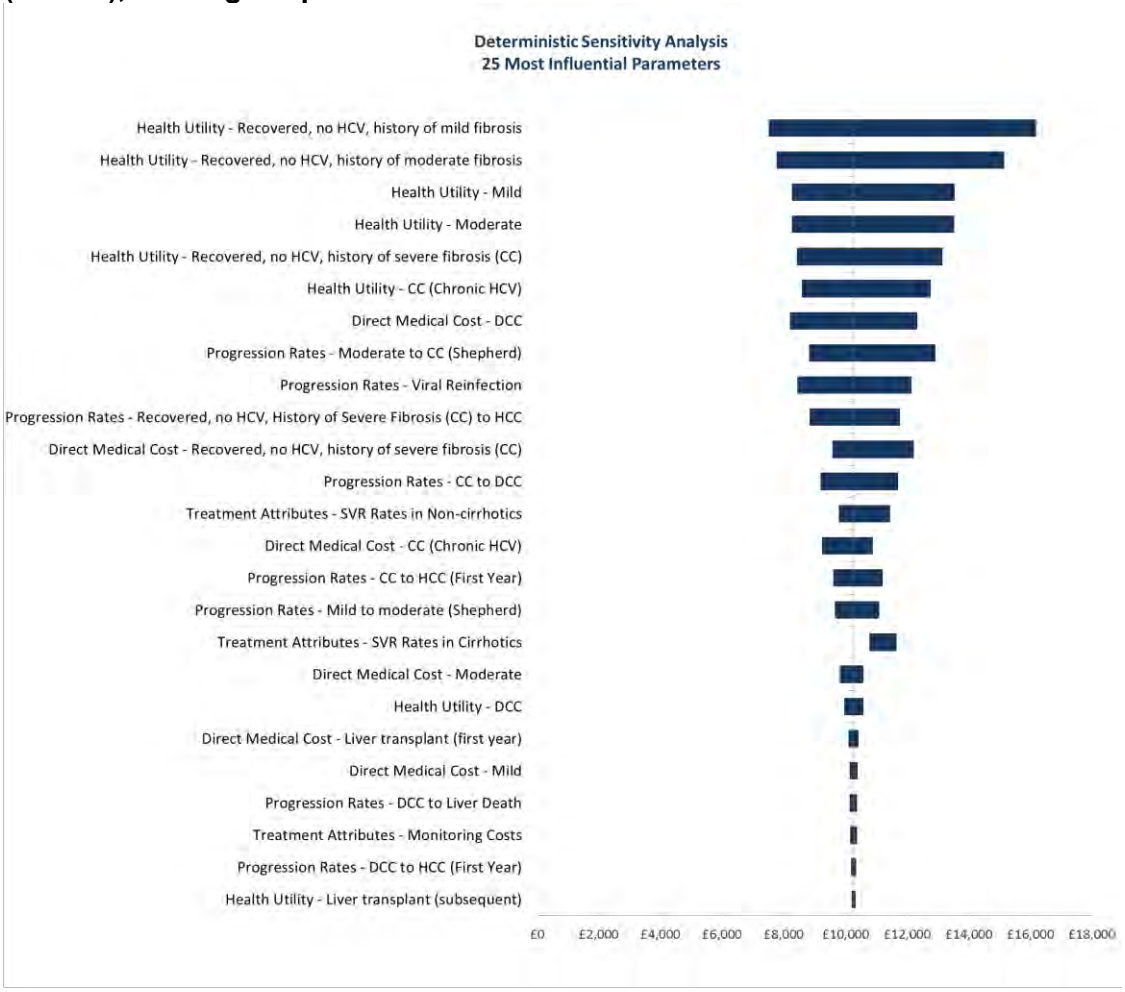
Figure 33: DSA AbbVie Regimen (3D) versus TPR + PR in GT1, treatment-experienced (overall), IFN-eligible patients



AbbVie Regimen versus PR in *GT1, Treatment-experienced (Overall), IFN-eligible Patients*

The base case ICER for the AbbVie Regimen compared with BOC + PR is £10,258/QALY. The tornado diagram is shown in the figure below. Health utility for the recovered, history of mild fibrosis, health utility for the recovered, history of moderate fibrosis and health utility for mild health state have the greatest impact on the results. However, the AbbVie Regimen has an ICER below £30,000/QALY in each analysis.

Figure 34: DSA AbbVie Regimen (3D) versus PR in GT1, treatment-experienced (overall), IFN-eligible patients

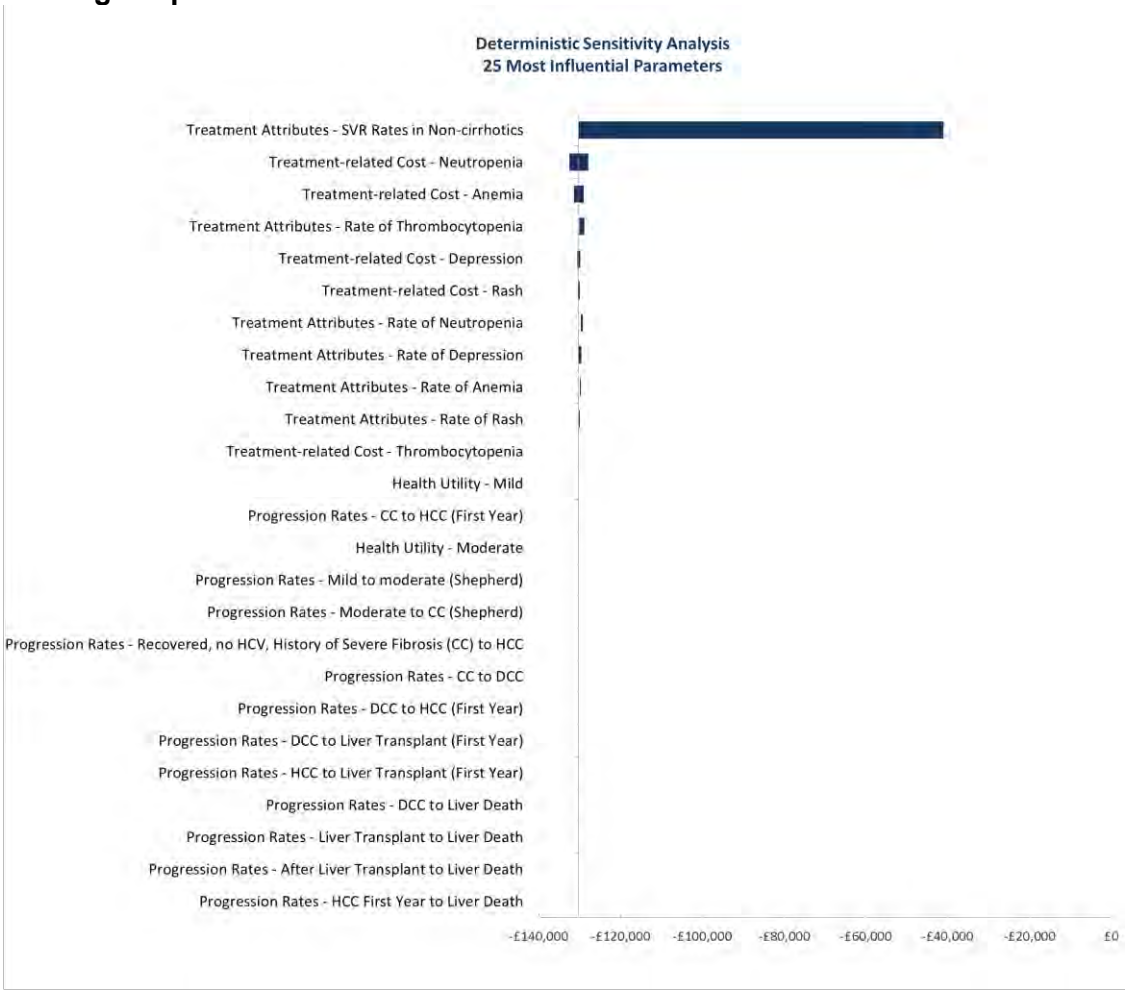


GT4, Treatment-Naive (Non-Cirrhotic) IFN-eligible Patients

AbbVie Regimen versus SOF + PR

The base case analysis shows AbbVie's 3D Regimen to be 'dominant' vs. SOF + PR (i.e., associated with lower costs and higher QALYs). The tornado diagram is shown in the figure below. SVR rates in non-cirrhotics, anaemia and neutropenia related costs have the greatest impact on the results, but the AbbVie Regimen remains 'dominant' in all scenarios.

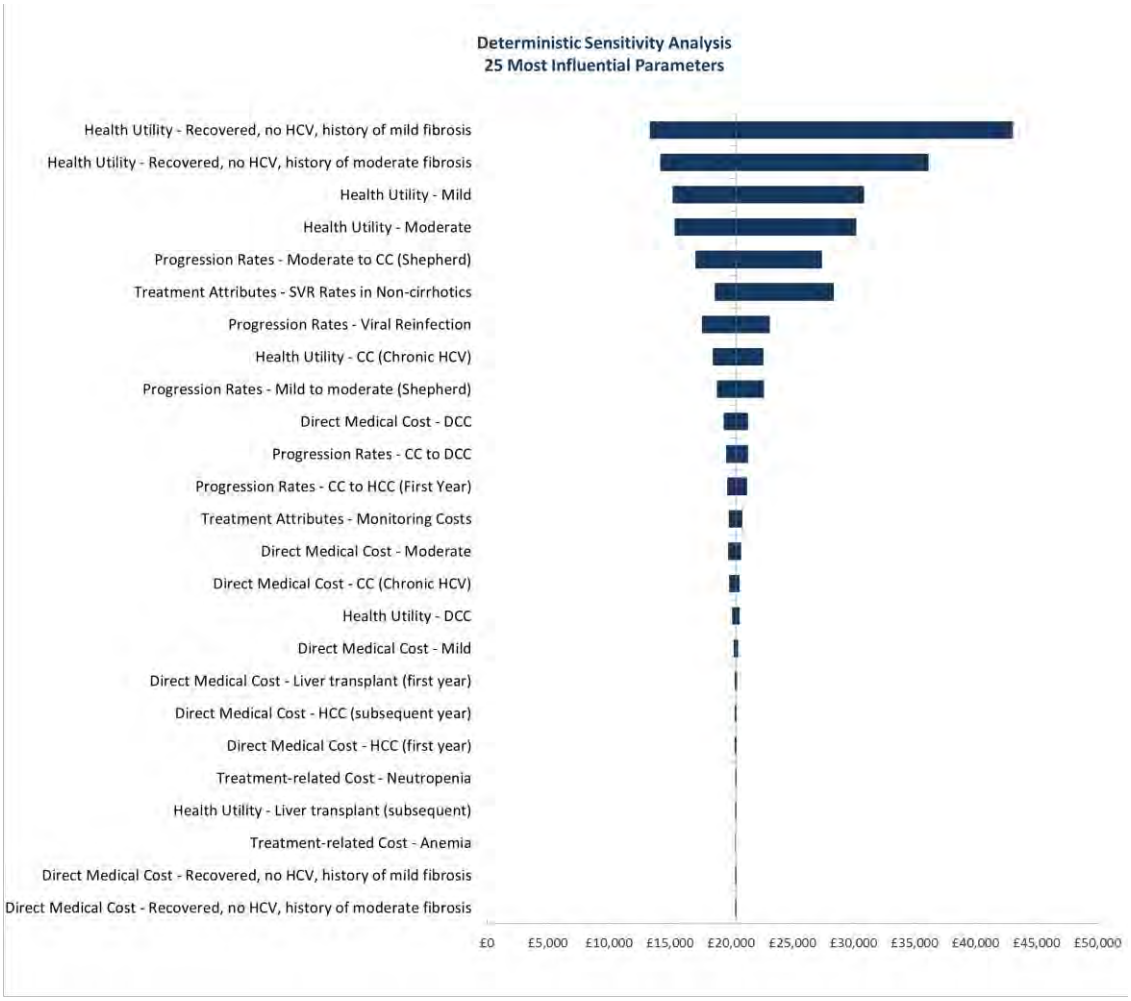
Figure 35: DSA AbbVie Regimen (2D) versus SOF+ PR in GT4, treatment-naive, IFN-eligible patients



AbbVie Regimen versus PR in *GT4, Treatment-Naive (Non-Cirrhotic) IFN-eligible Patients*

The base case ICER for AbbVie Regimen compared with PR is £20,351/QALY. The tornado diagram is shown in the figure below. Health utility for the recovered, history of mild fibrosis, health utility for the recovered, history of moderate fibrosis and health utility for mild health state have the greatest impact on the results tipping 2D's ICER above the £30,000/QALY threshold. AbbVie wishes to highlight that despite the uncertainty around the ICER demonstrated in this deterministic sensitivity analysis, consistent with the clinical trial findings in GT1 patients, SVR rate achieved by 2D in GT4 treatment-naïve, INF-eligible patients was 100%. This represents a step-change in treatment of patients infected with GT4 chronic hepatitis C for whom until recently, an antiviral therapy of choice was dual therapy with PR. As described in section 7.3.1, following conversion from the Ishak to the Metavir scoring system, the assumed PR SVR rate in our base-case was 70.6%. This rate was applied to both mild (F0-F1) and moderate (F2-F3) patients despite the fact that no patients with F3 fibrosis score were represented in the study sample, making our estimate a conservative one. AbbVie thus argues that the greater uncertainty observed in this patient segment compared to GT1 segment is primarily represented by the uncertainty in the clinical evidence for PR SVR rate estimates.

Figure 36: DSA AbbVie Regimen (2D) versus PR in GT4, treatment-naive, IFN-eligible patients

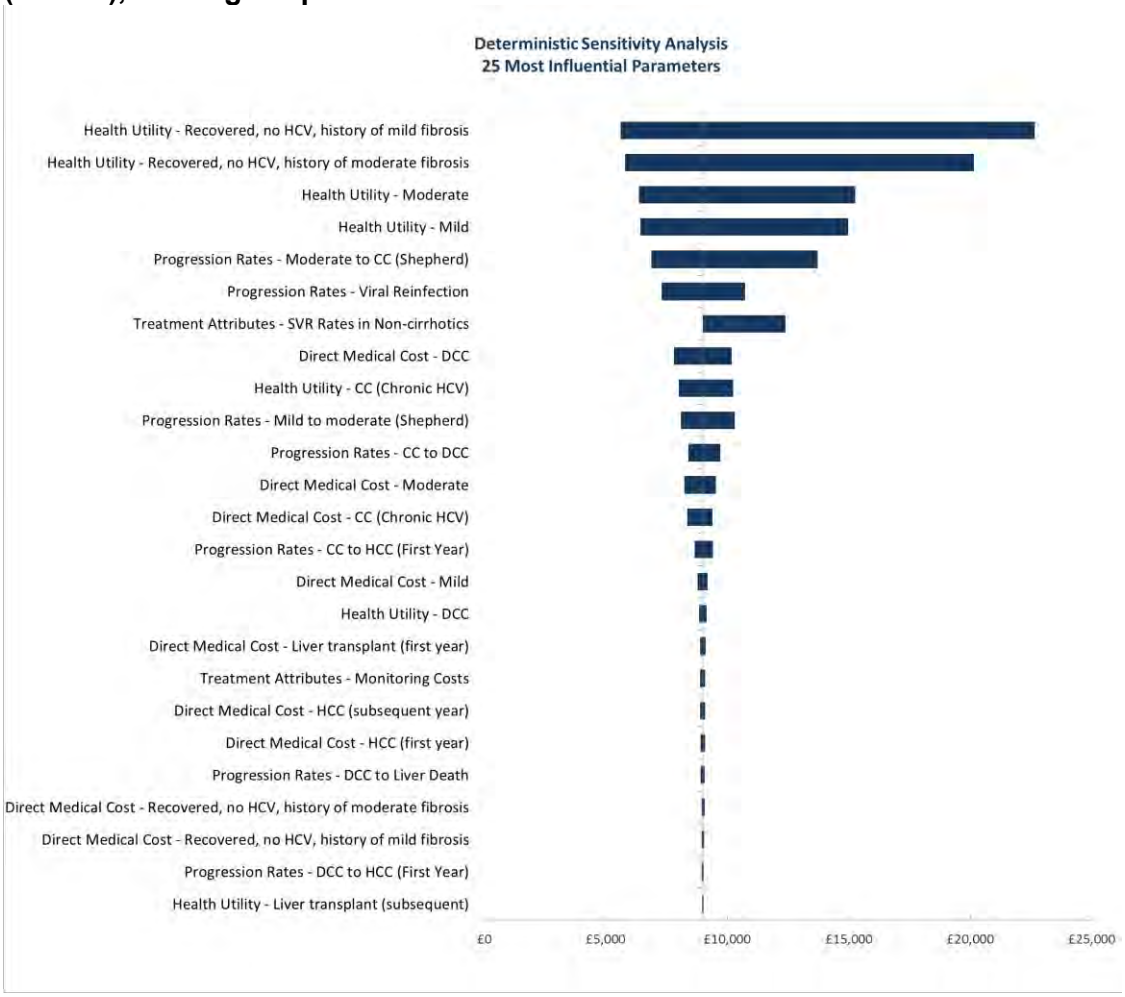


GT4, Treatment-Experienced (Non-Cirrhotic) IFN-eligible Patients

AbbVie Regimen versus No Treatment

The base case ICER for AbbVie Regimen compared with No treatment is £8,977/QALY. The tornado diagram is shown in the figure below. Health utility for the recovered, history of mild fibrosis, health utility for the recovered, history of moderate fibrosis and health utility for moderate fibrosis health state have the greatest impact on the results. 2D's ICER however remains below £30,000/QALY threshold in all scenarios.

Figure 37: DSA AbbVie Regimen (2D) versus PR in GT4, treatment-experienced (overall), IFN-eligible patients

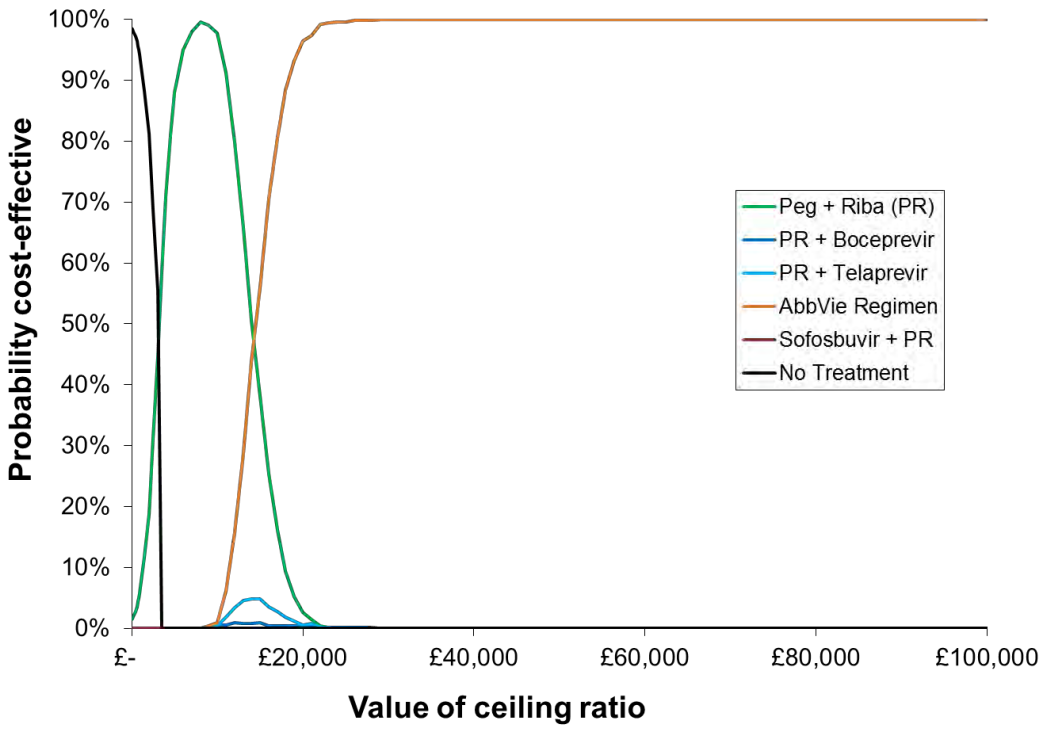


7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

PSA was performed on each patient segment, included 500 simulations and is represented below in the form of multiple comparisons or cost-effectiveness acceptability curves. Comparators not displayed in the CEA curves were the optimal choice in 0% of the simulations and were found optimal at no threshold. Although “No treatment” is not a comparator for IFN-eligible patient segments, it was added into the PSA for completeness.

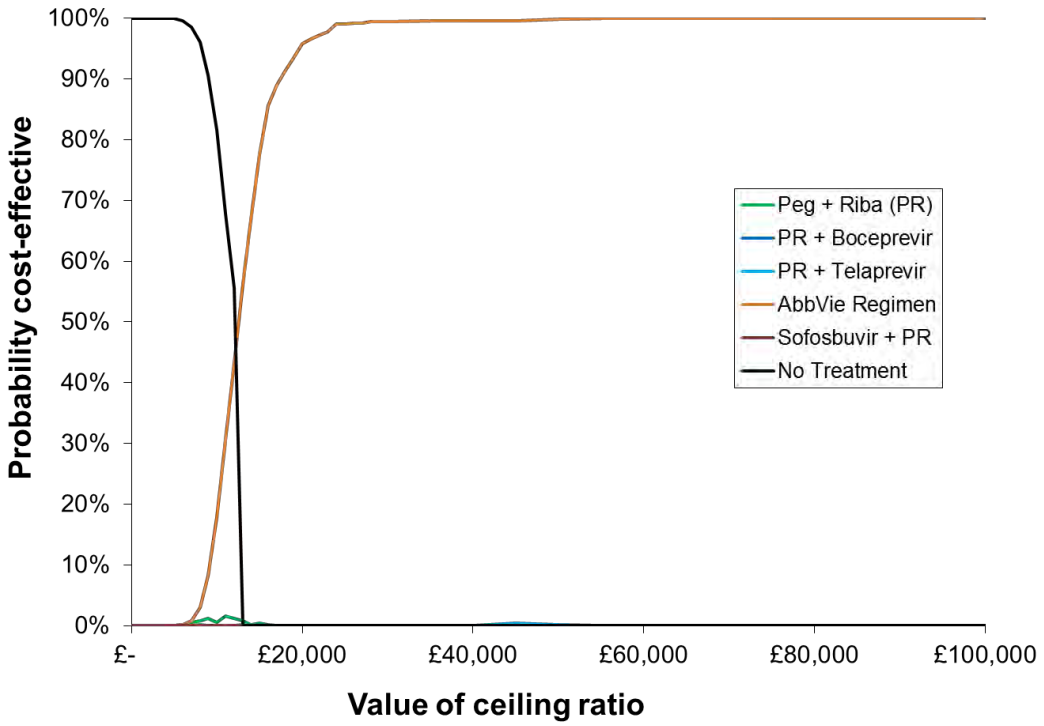
Probabilistic sensitivity analysis: multiple CEACs

Figure 38: GT1, treatment-naïve, IFN-eligible patients



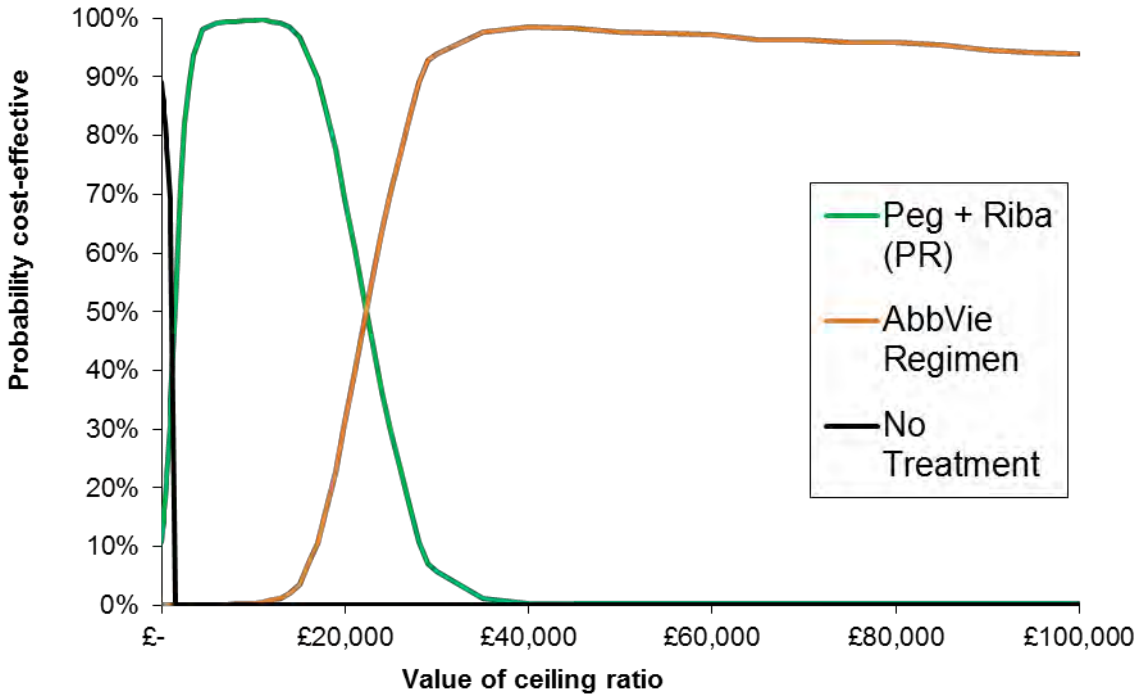
The AbbVie 3D Regimen is an optimal therapy if the payer is willing to pay more than £15,000/QALY. If the payer is willing to pay less than £15,000/QALY, PR (or no treatment) are optimal.

Figure 39: GT1, treatment-experienced (overall), IFN-eligible patients



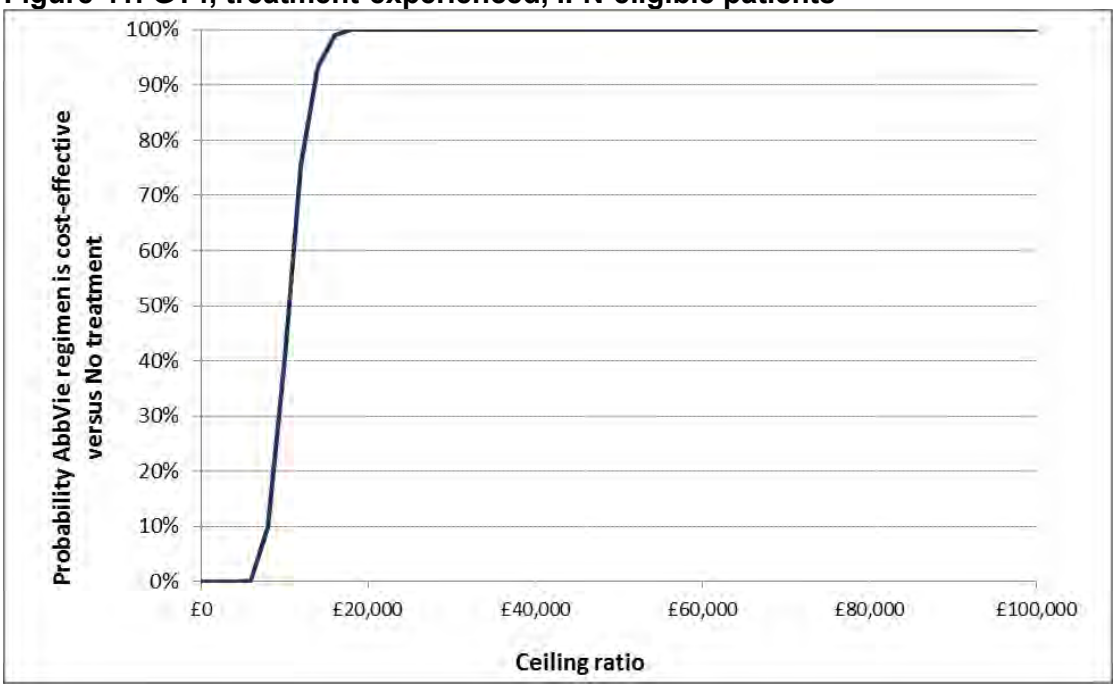
For HCV GT1 treatment-experienced patients, the AbbVie Regimen is the optimal therapy (on optimality frontier) if the payer is willing to pay more than £13,000/QALY. If the payer is willing to pay less than £13,000/QALY, no treatment is optimal.

Figure 40: GT4, treatment-naïve, IFN-eligible patients



For HCV GT4, at £23,000/QALY, AbbVie's 2D regimen has over 50% probability of being cost-effective.

Figure 41: GT4, treatment-experienced, IFN-eligible patients



At the payers' willingness to pay of £18,000/QALY, the probability of 2D being cost-effective versus no treatment is 100%.

7.7.9 **Please present the results of scenario analysis. Include details of structural sensitivity analysis.**

Scenario analyses were performed on the following 22 scenarios:

1. Scenario Analysis - Fibrosis Distribution (Lower Bound)
2. Scenario Analysis - Fibrosis Distribution (Upper Bound)
3. Scenario Analysis - Age (Lower Bound)
4. Scenario Analysis - Age (Upper Bound)
5. Scenario Analysis - % Male (Lower Bound)
6. Scenario Analysis - % Male (Upper Bound)
7. Scenario Analysis - % GT1a (50%)
8. Scenario Analysis - Grishchenko Transitional Probabilities
9. Scenario Analysis - Include Indirect Costs
10. Scenario Analysis - All Discount Rates (Lower Bound)
11. Scenario Analysis - All Discount Rates (Upper Bound)
12. Scenario Analysis - Time Horizon (30 Years)
13. Scenario Analysis - Therapy Duration (No Dropouts)
14. Scenario Analysis - Alternative SVR Estimates for PR (Hadzyannis)
15. Scenario Analysis - Alternative SVR Estimates for PR (McHutchinson)
16. Scenario Analysis - Alternative SVR Estimates for PR (Yee et al.)
17. Scenario Analysis - Alternative SVR Estimates for AbbVie (i.e., SVR stratified for mild and moderate fibrosis)
18. Scenario Analysis - Alternative SOF+PR Duration in CC Patients
19. Scenario Analysis - Health Utility - Vera-Llonch
20. Scenario Analysis - Health Utility - AbbVie UK Crosswalk

21. Scenario Analysis - 12 weeks of AbbVie therapy in GT1a cirrhotic patients with favourable baseline laboratory values

Findings are summarised in the table below.

Table 142: Summary of Scenario Analyses

Scenario Analysis 1: Fibrosis Distribution (Lower bound)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£15,610	15.83	NA	NA	NA	NA
Boceprevir + PR	£26,077	16.26	£10,468	0.43	£24,084	£5,718
Telaprevir + PR	£30,451	16.59	£14,841	0.76	£19,526	£3,924
AbbVie Regimen	£38,294	16.97	£22,684	1.15	£19,788	£5,924
Sofosbuvir + PR	£40,771	16.83	£25,161	1.00	£25,082	£8,464

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£16,018	14.34	NA	NA	NA	NA
Telaprevir + PR	£32,613	15.12	£16,595	0.78	£21,218	£9,123
AbbVie Regimen	£38,009	15.96	£21,991	1.62	£13,583	£3,325

Scenario Analysis 2: Fibrosis Distribution (Upper Bound)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£44,374	8.18	NA	NA	NA	NA
Telaprevir + PR	£55,132	9.11	£10,757	0.93	£11,560	-£4,042
Boceprevir + PR	£56,827	8.13	£12,453	-0.04	-£289,717	-£308,084
Sofosbuvir + PR	£61,777	9.73	£17,402	1.56	£11,182	-£5,436
AbbVie Regimen	£80,238	10.24	£35,864	2.07	£17,350	£3,485

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£46,482	7.33	NA	NA	NA	NA
Telaprevir + PR	£58,040	8.29	£11,557	0.96	£12,071	-£24
AbbVie Regimen	£78,890	9.81	£32,407	2.48	£13,060	£2,802

Scenario Analysis 3: Age (Lower Bound)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£23,750	14.33	NA	NA	NA	NA
Boceprevir + PR	£32,859	14.89	£9,109	0.56	£16,355	-£2,012
Telaprevir + PR	£36,518	15.25	£12,768	0.92	£13,927	-£1,675
AbbVie Regimen	£44,086	15.97	£20,336	1.64	£12,396	-£1,468
Sofosbuvir + PR	£44,844	15.75	£21,094	1.42	£14,874	-£1,744

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£32,542	12.06	NA	NA	NA	NA
Telaprevir + PR	£44,385	13.34	£11,843	1.28	£9,281	-£2,814
AbbVie Regimen	£53,127	14.63	£20,585	2.57	£8,024	-£2,234

Scenario Analysis 4: Age (Upper Bound)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£19,460	11.14	NA	NA	NA	NA
Boceprevir + PR	£29,433	11.48	£9,973	0.34	£29,451	£11,084
Telaprevir + PR	£33,531	11.7	£14,071	0.57	£24,888	£9,286
AbbVie Regimen	£42,049	12.16	£22,589	1.03	£22,012	£8,148
Sofosbuvir + PR	£42,552	12.02	£23,092	0.88	£26,280	£9,662

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£26,740	9.63	NA	NA	NA	NA
Telaprevir + PR	£40,296	10.4	£13,557	0.77	£17,626	£5,531
AbbVie Regimen	£50,347	11.25	£23,608	1.62	£14,539	£4,281

Scenario Analysis 5: % Male (Lower Bound)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£22,906	13.74	NA	NA	NA	NA
Boceprevir + PR	£32,174	14.25	£9,268	0.51	£18,286	-£80
Telaprevir + PR	£35,911	14.58	£13,004	0.84	£15,535	-£67
AbbVie Regimen	£43,641	15.24	£20,735	1.5	£13,805	-£59
Sofosbuvir + PR	£44,356	15.04	£21,450	1.3	£16,548	-£70

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£30,180	11.09	NA	NA	NA	NA
Telaprevir + PR	£42,682	12.13	£12,503	1.04	£12,029	-£66
AbbVie Regimen	£51,906	13.22	£21,727	2.13	£10,206	-£52

Scenario Analysis 6: % Male (Upper Bound)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£22,838	13.69	NA	NA	NA	NA
Boceprevir + PR	£32,119	14.2	£9,281	0.5	£18,446	£80
Telaprevir + PR	£35,863	14.52	£13,024	0.83	£15,669	£67
AbbVie Regimen	£43,608	15.18	£20,769	1.49	£13,923	£59
Sofosbuvir +	£44,319	14.98	£21,480	1.29	£16,688	£70

PR						

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£30,076	11.04	NA	NA	NA	NA
Telaprevir + PR	£42,610	12.07	£12,534	1.03	£12,161	£66
AbbVie Regimen	£51,858	13.16	£21,781	2.11	£10,310	£52

Scenario Analysis 7: % GT1a (50%)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£22,872	13.72	NA	NA	NA	NA
Boceprevir + PR	£32,147	14.22	£9,275	0.5	£18,366	£0
Telaprevir + PR	£35,887	14.55	£13,014	0.83	£15,602	£0
AbbVie Regimen	£42,729	15.24	£19,857	1.52	£13,076	-£789
Sofosbuvir + PR	£44,337	15.01	£21,465	1.29	£16,618	£0

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£30,128	11.07	NA	NA	NA	NA
Telaprevir + PR	£42,646	12.1	£12,518	1.04	£12,095	£0
AbbVie Regimen	£49,671	13.2	£19,543	2.13	£9,175	-£1,083

Scenario Analysis 8: Grishchenko Transitional Probabilities

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£22,359	13.82	NA	NA	NA	NA
Boceprevir + PR	£31,792	14.29	£9,433	0.47	£19,917	£1,551
Telaprevir + PR	£35,602	14.6	£13,243	0.79	£16,782	£1,180
AbbVie Regimen	£43,499	15.24	£21,140	1.42	£14,889	£1,025
Sofosbuvir +	£44,171	15.04	£21,812	1.22	£17,838	£1,220

PR						

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£29,620	11.16	NA	NA	NA	NA
Telaprevir + PR	£42,394	12.15	£12,774	0.99	£12,931	£836
AbbVie Regimen	£51,801	13.2	£22,181	2.04	£10,861	£603

Scenario Analysis 9: Include Indirect Costs

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£48,906	13.72	NA	NA	NA	NA
AbbVie Regimen	£51,021	15.21	£2,115	1.5	£1,413	-£12,452
Telaprevir + PR	£52,427	14.55	£3,521	0.83	£4,221	-£11,381
Boceprevir + PR	£53,791	14.22	£4,885	0.5	£9,674	-£8,693
Sofosbuvir + PR	£54,733	15.01	£5,826	1.29	£4,511	-£12,107

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
AbbVie Regimen	£62,877	13.19	NA	NA	NA	£10,258
Telaprevir + PR	£69,305	12.1	£6,428	-1.09	-£5,921	-£18,015
PR	£70,559	11.07	£7,682	-2.12	-£3,622	NA

Note: PR no longer least expensive option in this scenario; interpret "Change from Basecase" accordingly.

Scenario Analysis 10: All Discount Rates (Lower Bound)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£37,367	25.14	NA	NA	NA	NA
Boceprevir + PR	£43,688	26.32	£6,321	1.18	£5,351	-£13,016
Telaprevir + PR	£45,839	27.07	£8,472	1.93	£4,388	-£11,214
AbbVie	£50,150	28.55	£12,784	3.42	£3,741	-£10,123

Regimen						
Sofosbuvir + PR	£51,796	28.11	£14,429	2.98	£4,849	-£11,769

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£47,725	18.71	NA	NA	NA	NA
Telaprevir + PR	£54,736	20.99	£7,011	2.27	£3,082	-£9,013
AbbVie Regimen	£59,455	23.16	£11,730	4.45	£2,637	-£7,621

Scenario Analysis 11: All Discount Rates (Upper Bound)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£18,410	9.94	NA	NA	NA	NA
Boceprevir + PR	£28,602	10.26	£10,193	0.32	£31,923	£13,557
Telaprevir + PR	£32,871	10.47	£14,462	0.53	£27,294	£11,692
AbbVie Regimen	£41,745	10.9	£23,335	0.96	£24,225	£10,361
Sofosbuvir + PR	£42,142	10.76	£23,733	0.82	£28,788	£12,170

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£23,977	8.31	NA	NA	NA	NA
Telaprevir + PR	£38,465	8.96	£14,488	0.66	£22,019	£9,924
AbbVie Regimen	£49,391	9.71	£25,415	1.41	£18,037	£7,779

Scenario Analysis 12: Time Horizon (30 Years)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£20,328	11.98	NA	NA	NA	NA
Boceprevir + PR	£30,110	12.34	£9,782	0.36	£27,117	£8,751
Telaprevir + PR	£34,084	12.58	£13,757	0.6	£22,772	£7,170
AbbVie	£42,330	13.07	£22,002	1.09	£20,097	£6,232

Regimen						
Sofosbuvir + PR	£42,911	12.91	£22,583	0.94	£24,070	£7,452

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£27,825	10.14	NA	NA	NA	NA
Telaprevir + PR	£40,998	10.94	£13,173	0.8	£16,414	£4,320
AbbVie Regimen	£50,687	11.83	£22,862	1.69	£13,525	£3,267

Scenario Analysis 13: Therapy Duration (No Dropouts)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£25,476	13.72	NA	NA	NA	NA
Boceprevir + PR	£36,235	14.22	£10,759	0.5	£21,306	£2,940
Telaprevir + PR	£40,165	14.55	£14,689	0.83	£17,610	£2,008
AbbVie Regimen	£43,962	15.21	£18,487	1.5	£12,351	-£1,514
Sofosbuvir + PR	£44,739	15.01	£19,263	1.29	£14,914	-£1,705

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£33,655	11.07	NA	NA	NA	NA
Telaprevir + PR	£49,130	12.1	£15,475	1.04	£14,952	£2,857
AbbVie Regimen	£52,471	13.19	£18,816	2.12	£8,873	-£1,385

Scenario Analysis 14: Alternative SVR Estimates for PR (Hadzyannis)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£21,265	14	NA	NA	NA	NA
Boceprevir + PR	£32,147	14.22	£10,882	0.23	£48,192	£29,825

Telaprevir + PR	£35,887	14.55	£14,621	0.55	£26,346	£10,744
AbbVie Regimen	£43,624	15.21	£22,359	1.22	£18,363	£4,499
Sofosbuvir + PR	£44,337	15.01	£23,072	1.01	£22,787	£6,169

Scenario Analysis 15: Alternative SVR Estimates for PR (McHutchinson)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
Peg + Riba (PR)	£23,161	13.67	NA	NA	NA	NA
PR + Boceprevir	£32,147	14.22	£8,986	0.55	£16,249	-£2,117
PR + Telaprevir	£35,887	14.55	£12,726	0.88	£14,425	-£1,177
AbbVie regimen	£43,624	15.21	£20,463	1.54	£13,246	-£618
Sofosbuvir + PR	£44,337	15.01	£21,176	1.34	£15,807	-£811

Scenario Analysis 16: Alternative SVR Estimates for PR in GT4 (Yee et al.)

Genotype 4 treatment-naïve interferon eligible (non-cirrhotics only)

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£20,593	14.76	NA	NA	NA	NA
AbbVie Regimen	£36,490	15.84	£15,897	1.08	£14,691	-£5,660
Sofosbuvir + PR	£41,237	15.81	£20,643	1.05	£19,742	-£7,393

Genotype 4 treatment-experienced (overall) interferon eligible (non-cirrhotics only)

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. NT (Scenario)	Change from Basecase
No treatment	£16,186	12.58	NA	NA	NA	NA
AbbVie Regimen	£36,536	14.84	£20,350	2.27	£8,977	£1,364

Scenario Analysis 17: Alternative SVR Estimates for AbbVie (i.e., SVR stratified for mild and moderate fibrosis)

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase

PR	£22,872	13.72	NA	NA	NA	NA
Boceprevir + PR	£32,147	14.22	£9,275	0.5	£18,366	£0
Telaprevir + PR	£35,887	14.55	£13,014	0.83	£15,602	£0
AbbVie Regimen	£43,724	15.2	£20,852	1.48	£14,048	£183
Sofosbuvir + PR	£44,337	15.01	£21,465	1.29	£16,618	£0

Scenario Analysis 18: Alternative SOF+PR Duration in CC Patients

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£22,872	13.72	NA	NA	NA	NA
Boceprevir + PR	£32,147	14.22	£9,275	0.5	£18,366	£0
Telaprevir + PR	£35,887	14.55	£13,014	0.83	£15,602	£0
AbbVie Regimen	£43,624	15.21	£20,752	1.5	£13,864	£0
Sofosbuvir + PR	£47,345	15.01	£24,473	1.29	£18,947	£2,329

Scenario Analysis 19: Health Utility – Vera Llonch

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£22,872	13.58	NA	NA	NA	NA
Boceprevir + PR	£32,147	14.03	£9,275	0.45	£20,731	£2,365
Telaprevir + PR	£35,887	14.32	£13,014	0.74	£17,635	£2,033
AbbVie Regimen	£43,624	14.91	£20,752	1.33	£15,607	£1,742
Sofosbuvir + PR	£44,337	14.73	£21,465	1.15	£18,739	£2,121

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£30,128	11.02	NA	NA	NA	NA
Telaprevir + PR	£42,646	11.92	£12,518	0.9	£13,896	£1,801
AbbVie Regimen	£51,882	12.88	£21,754	1.87	£11,659	£1,401

Scenario Analysis 20: Health Utility - AbbVie EQ5D UK Crosswalk

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£22,872	16.29	NA	NA	NA	NA
Boceprevir + PR	£32,147	16.67	£9,275	0.38	£24,148	£5,782
Telaprevir + PR	£35,887	16.93	£13,014	0.65	£20,136	£4,534
AbbVie Regimen	£43,624	17.52	£20,752	1.23	£16,875	£3,010
Sofosbuvir + PR	£44,337	17.34	£21,465	1.05	£20,476	£3,858

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£30,128	13.44	NA	NA	NA	NA
Telaprevir + PR	£42,646	14.18	£12,518	0.74	£16,863	£4,768
AbbVie Regimen	£51,882	15.11	£21,754	1.66	£13,076	£2,818

Scenario Analysis 21: 12 weeks of AbbVie therapy in GT1a cirrhotic patients with favorable baseline laboratory values

Genotype 1 treatment-naïve interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£22,872	13.72	NA	NA	NA	NA
Boceprevir + PR	£32,147	14.22	£9,275	0.5	£18,366	£0
Telaprevir + PR	£35,887	14.55	£13,014	0.83	£15,602	£0
AbbVie Regimen	£41,929	15.21	£19,057	1.49	£12,762	-£1,102
Sofosbuvir + PR	£44,337	15.01	£21,465	1.29	£16,618	£0

Genotype 1 treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER vs. PR (Scenario)	Change from Basecase
PR	£30,128	11.07	NA	NA	NA	NA
Telaprevir + PR	£42,646	12.1	£12,518	1.04	£12,095	£0
AbbVie Regimen	£47,535	13.16	£17,407	2.1	£8,301	-£1,957

7.7.10 What were the main findings of each of the sensitivity analyses?

As stated in Section 7.7.7, in the deterministic sensitivity analysis comparing AbbVie regimen (3D) versus SOF + PR in GT1, treatment-naïve, IFN-eligible patients, the cost of DCC, health utility for the recovered, history of mild HCV, and health utility for the recovered, history of moderate HCV have the greatest impact on the results. However, the AbbVie Regimen remains 'dominant' versus SOF + PR in all scenarios.

In the DSA versus either dual or triple PR containing regimens, health utility for the recovered, history of moderate HCV and recovered, history of mild HCV, and health utilities of mild and moderate health states have the greatest impact on the results. The AbbVie Regimen however achieves an ICER below £30,000/QALY in each analysis versus each comparator.
An ICER below £30,000/QALY for AbbVie regimen is also maintained in each of the 22 scenario analyses.

Therefore to summarise, the incremental cost/QALY results across both genotypes (GT1 and GT4) and patient segments (treatment-naïve or experienced) remain the most sensitive to the health utility values for the progressive disease health states (mild and moderate) and their associated recovered (SVR) health states.

In the multiple probabilistic sensitivity analysis conducted on GT1 patients (naïve and experienced overall; IFN-eligible), the AbbVie 3D Regimen has shown to be the therapy of choice when payers are willing to pay above £13,000/QALY. In comparison with SOF+PR regimen, it dominates as it is less costly and more beneficial. In GT4 treatment-naïve, IFN-eligible patients, 2D is the therapy of choice when payers are willing to pay above £20,000/QALY. In GT4 treatment-experienced (overall), IFN-eligible patients, the probability of 2D being cost-effective at £20,000/QALY versus no treatment is 100%. The AbbVie 3D and 2D Regimens thus represent good value for money for the NHS in England and Wales for the treatment of both GT1 and GT4 chronic hepatitis C patients.

7.7.11 What are the key drivers of the cost-effectiveness results?

Compared to all comparators, the AbbVie Regimen demonstrated superior efficacy, less treatment-related disutility and better tolerability giving rise to improved treatment and patient outcomes. Thus the results of the cost-effectiveness modelling show that the antiviral therapy with 3D or 2D is associated with higher QALYs gains despite increased treatment cost. For a more detailed response, please see relevant sections above.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

AbbVie assessed model validity in terms of technical validation, internal validation and external validation.

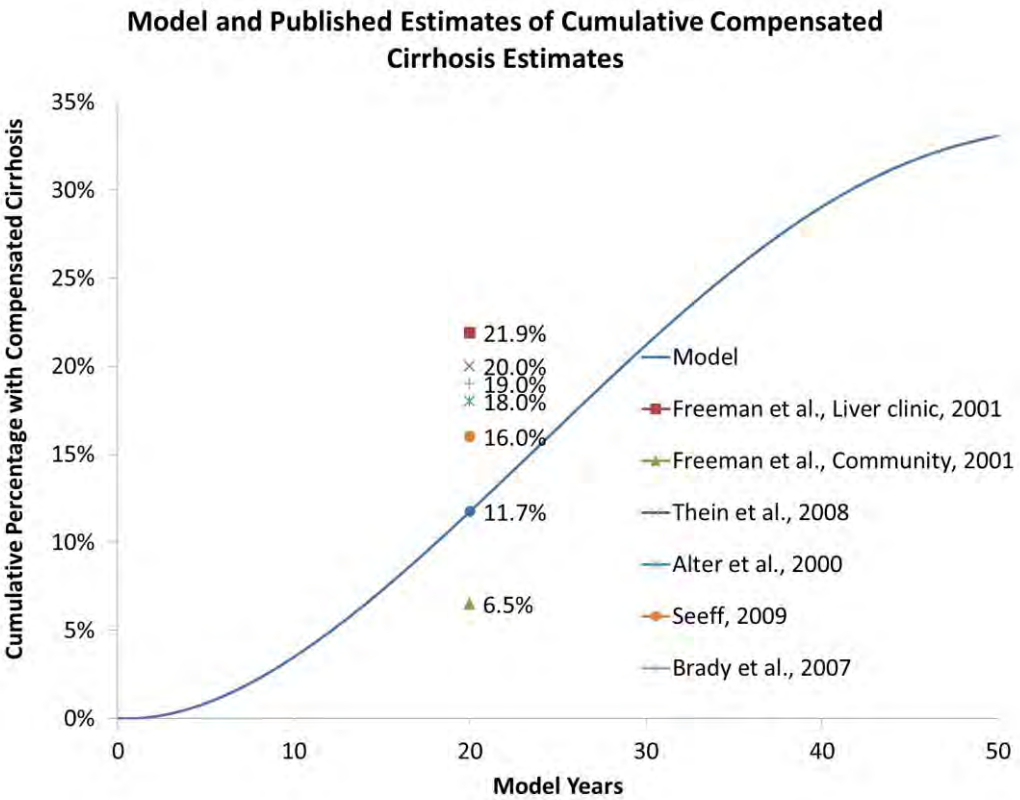
Technical and internal validation

Technical validation involved checking the software program and cleaning it for potential programming errors. Validation using different routine tests yielded the expected results. An experienced, independent modeling team at an academic institution in Austria also reviewed our model structure and parameters. Internal validation involved comparing the model's predictions with the data that was used.

External validation: AbbVie HCV model estimates of compensated cirrhosis in untreated patients

To assess external validity of the model, the model's estimates of compensated cirrhosis in untreated patients (i.e., setting treatment to "No Treatment") with mild disease ((i.e., setting Initial Fibrosis Distribution to 100% mild) were generated. The base case (Age 40, 70% male) uses Shepherd et al. (2007) fibrosis progression rates, and predicts 11.7% of patients have ever had compensated cirrhosis at 20 years. Compensated cirrhosis rate estimates over fifty years appear in the following figure, which also includes cirrhosis estimates from other sources (explained in detail below).

Figure 42: Model estimates and estimates from the literature of cumulative CC rates



The Shepherd et al. (2007) fibrosis rates, used in this model's base case and also in Hartwell et al. (2011) are based on research done by Wright et al. (2006). Though the Shepherd et al. (2007) and Hartwell et al. (2011) studies do not provide their models' estimates of disease progression at 20+ years, we assume their figures would be similar to those reported in Wright et al. (2006). Wright et al. (2006) reports

that the "probability of staying cirrhosis free for the main group of interest was predicted to be about 0.8 after 30 years of infection." In our model, the similar figure is 0.788 (i.e., 21.2% develop compensated cirrhosis at 30 years in the no treatment scenario with initial fibrosis at 100% mild fibrosis).

Clinical literature and prior model estimates of compensated cirrhosis in untreated patients

Wright et al. (2006) discussed the systematic review of fifty-seven epidemiological studies reported in Freeman et al. (2001).[124] Each of the fifty-seven studies had a different mean duration of infection for the study subjects, ranging from 3 to 26 years. The authors divided the published studies into four categories according to their population: liver clinic series, post-transfusion studies, blood donor studies and community-based studies. The authors estimated the prevalence of cirrhosis at 20 years for each study and then estimated the mean prevalence of cirrhosis for each group of studies. After 20 years of infection with HCV, the mean proportion of cases with cirrhosis was 21.9% in the liver clinic series (N=482), 23.8% in the post-transfusion cohorts (N=72), 3.7% for the blood donor series (N=65) and 6.5% for the community-based cohorts (N=231). We include the liver clinic series and community-based cohorts in the comparison figure, given their larger sample sizes.

Aside from Freeman et al. (2001), two clinical literature review articles, Alter and Seeff (2000)[125], Seeff (2009)[126], one systematic meta-analysis, Thein et al. (2008)[127], and one model, Brady et al. (2007)[128], were selected for comparison.

Alter and Seeff (2000) summarised the existing literature on the natural progression of HCV in 2000. They found thirteen analyses with varying study designs (i.e., retrospective, prospective, and cohort), which examined the presence of cirrhosis in patients with interval exposure ranging from 7 to 50 years. Of the twelve studies that examined adult patients, rates of cirrhosis varied from 2% to 55% at the end of follow-up. The authors then synthesised the data to provide point estimates for the long-term natural progression of HCV. The progression to a severe clinical outcome, defined as cirrhosis and/or HCC, was approximated at about 20% at 20 years (per Figure 3. "The percent with severe outcomes in the first two decades of infection is based on a considerable body of evidence (see text) and appears to be less than 20%" (p. 31).)

A follow-up study by Seef (2009) estimated cirrhosis in their mild patient cohort at 20 years after infection was "16% overall, 18% for cross-sectional/retrospective and 7% for retrospective-prospective studies, 18% for studies in clinical settings and 7% for studies conducted in non-clinical settings."

A meta-analysis by Thein et al. (2008), which aggregated data from primary trials, synthesised 111 reported natural history studies to quantify the rate of cirrhosis in chronic HCV patients. The meta-analysis concluded that the estimated prevalence of cirrhosis in HCV patients at 20 years after infection is 20%.

Other articles indicate a similar progression rate. The progression of untreated HCV infection to cirrhosis is often cited to be approximately 20% within 20 years of disease, which is primarily based on figures taken from prospective studies published in the early to mid-1990s. In the literature reviews and meta-analyses summarising data from multiple trials, the overall range of progression to cirrhosis varied from 15% to 25% at 20 years follow-up.

Brady et al. (2007) developed a model to project natural progression to cirrhosis for HCV patients for an economic evaluation of peg-IFN plus ribavirin for chronic HCV treatment for CADTH. Brady et al. (2007) conducted formal validation analyses. Their model projects a progression to cirrhosis in 19% of HCV patients at 20 years. They also performed a review of published prospective studies to assess external validity, and determined progression to cirrhosis to be about 20% at 20 years among HCV patients.

There are limitations to these analyses. Prevalence is sometimes unclearly reported as conditional on being alive or not. Date of infection is often imprecisely known. Studies may measure time from acute or chronic infection.

In summary, our model is based on the Hartwell et al. (2011) and Shepherd et al. (2007) models, and aligns with Wright et al. (2006) the original source of the fibrosis probabilities. Other models and clinical literature have assumed a faster baseline rate of progression than our model.

7.9 Subgroup analysis

7.9.1 **Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.**

The final scope for this appraisal stated that the following sub-groups should be explored if evidence allows:

- (sub)Genotype
- Patients with and without cirrhosis
- Response to previous treatment (non-response, partial response, relapsed)
- People who are intolerant to or ineligible for IFN-treatment
- Patients co-infected with HIV
- People who have received treatment pre- and post-liver transplant

The cost-effectiveness results of 3D in the population infected with sub-genotypes GT1a and GT1b, population with cirrhosis, population unsuitable for IFN-based regimens, and subgroups based on the modality of prior non-response to PR are presented in section 7.9.4 of the submission.

In order to maximise treatment outcomes of patients treated with AbbVie's regimen, sub-genotyping has to be performed. This will ensure that patients are matched to appropriate combinations of DAAs indicated to treat either GT1a or GT1b. Data from comparator regimen trials also show disparity in the rates of response (SVR) in GT1a and GT1b infected patients, thus supporting this stratification.

Chronic HCV GT1 patients co-infected with HIV have a greater risk of more rapid progression of liver disease compared to mono-infected patients and therefore have an even greater need for HCV treatment. As discussed early on in the submission (Section 1.6 and section 6.5.1.9), AbbVie conducted a randomised, open-label study to evaluate the safety and efficacy of 3D co-administered with RBV for the treatment of HCV GT1 and HIV co-infection. As the patient characteristics, SVR rates and AEs for HCV-HIV co-infected patients approximate those observed in mono-infected patients, no specific modelling was conducted for co-infected patients. It can therefore be assumed that 3D would be similarly cost-effective in co-infected patients compared to current treatment options and the results generated for mono-infected patients can be extended to patients co-infected with HIV.

A similar approach was taken for post-transplant patients who were not modelled due to the lack of an appropriate modelling framework specific to post transplant patients. Given the high SVR rates achieved in the CORAL-1 study in post-transplant patients (see Section 6.5.1.10); it is plausible to assume that the cost-effectiveness results would be similar to the results of patients with mild or moderate fibrosis. However, there is limited availability of the epidemiology data upon which to base this assumption and therefore to model outcomes in this population.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

All patient segments identified above as subgroups in the NICE final scope have had consistently high SVR rates observed across all AbbVie's Phase III trials. Of note, given that the AbbVie regimen is IFN-free, history of intolerance to- or ineligibility to IFN was not captured as part of patients' baseline characteristics in AbbVie's trials. HIV co-infected, cirrhotic patients and Gt1a and GT1b patients were assessed in TURQUOISE I and II trials, PEARL IV and PEARL III trials respectively and were not treated as subgroups in Phase III development, but rather their own population entities. Characteristics of these patients and other subgroups are described in Section 6.3.4 of the submission.

Given that AbbVie's Phase III development involved multinational clinical trials, patients' baseline characteristics derived from the trials were not deemed generalizable to the likely eligible population in the UK setting. Therefore, baseline characteristics of the modelled cohorts were based on the UK clinical audit undertaken at a London teaching hospital (reported in detail by Hartwell et al 2011 and described in section 7.2 of the submission) differentiating between new and existing patients (treatment-naïve and experienced) in terms of average age, gender distribution as well as the distribution of patients across stages of chronic liver disease. Clinical expert advisors to this submission confirmed that the assumed baseline characteristics agreed with their clinical experience.

7.9.3 Please describe how the statistical analysis was undertaken.

N/A.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

The cost-effectiveness results for the above selected patients subgroups are presented in the series of tables below in the same manner they were presented in the base-case.

Table 143: Incremental analysis for GT1a, treatment-naïve (IFN-eligible) patients

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£23,305	19.63	13.64	NA	NA	NA	NA	NA
Boceprevir + PR	£32,905	19.86	14.09	£9,601	0.22	0.45	£21,411	Extended dominance
Telaprevir + PR	£36,378	20.10	14.47	£13,073	0.47	0.82	£15,865	Extended dominance
Sofosbuvir + PR	£44,064	20.49	15.06	£20,760	0.85	1.41	£14,680	Extended dominance
AbbVie Regimen	£45,110	20.57	15.18	£21,805	0.93	1.54	£14,199	£14,199

Table 144: Incremental analysis for GT1b, treatment-naïve (IFN-eligible) patients

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

Table 145: GT1a, treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£29,458	17.22	11.16	NA	NA	NA	NA	NA
Telaprevir + PR	£43,559	17.81	11.96	£14,101	0.59	0.80	£17,543	Extended dominance
AbbVie	£55,552	18.71	13.17	£26,093	1.50	2.01	£12,978	£12,978

Regimen

Table 146: GT1b, treatment-experienced (overall) interferon eligible

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£30,738	17.06	10.98	NA	NA	NA	NA	NA
Telaprevir + PR	£41,579	18.04	12.26	£10,841	0.98	1.28	£8,474	Extended dominance
AbbVie Regimen	£43,790	18.72	13.22	£13,052	1.66	2.24	£5,828	£5,828
PR								

Table 147: GT1, treatment-experienced (null responders) interferon eligible

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£31,630	16.98	10.82	NA	NA	NA	NA	NA
Telaprevir + PR	£47,701	17.34	11.29	£16,072	0.36	0.47	£34,310	Extended dominance
AbbVie Regimen	£52,089	18.69	13.16	£20,459	1.70	2.34	£8,755	£8,755

Table 148: GT1, treatment-experienced (partial responders) interferon eligible

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£29,486	17.23	11.11	NA	NA	NA	NA	NA
Telaprevir + PR	£43,041	17.80	12.10	£13,555	0.57	1.00	£13,622	Extended dominance
Boceprevir + PR	£47,403	17.32	11.48	£17,917	0.09	0.38	£47,644	Extended dominance
AbbVie Regimen	£51,770	18.72	13.21	£22,284	1.48	2.11	£10,584	£10,584

Table 149: treatment-experienced (prior relapsers) interferon eligible

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. PR	ICER incremental
PR	£29,483	17.17	11.22	NA	NA	NA	NA	NA
Telaprevir + PR	£38,558	18.43	12.71	£9,075	1.26	1.49	£6,091	£6,091
Boceprevir + PR	£42,763	17.86	12.18	£13,280	0.69	0.96	£13,875	Dominated
AbbVie Regimen	£51,811	18.74	13.19	£22,328	1.56	1.97	£11,334	£27,601

Table 150: GT1, treatment-naïve interferon unsuitable

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. NT	ICER incremental
No treatment	£19,788	19.01	12.70	NA	NA	NA	NA	NA
AbbVie Regimen	£43,624	20.59	15.21	£23,837	1.58	2.51	£9,498	£9,498

Table 151: GT1, treatment-experienced (overall) interferon unsuitable

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. NT	ICER incremental
No treatment	£24,245	16.84	10.80	NA	NA	NA	NA	NA
AbbVie Regimen	£51,882	18.72	13.19	£27,637	1.88	2.38	£11,597	£11,597

Table 152: GT4, treatment-naïve interferon unsuitable (non-cirrhotics only)

Regimen	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYGs	Incremental QALYs	ICER vs. NT	ICER incremental
No treatment	£17,230	19.62	13.31	NA	NA	NA	NA	NA
AbbVie Regimen	£36,490	20.98	15.84	£19,260	1.36	2.53	£7,614	£7,614

NT denotes No Treatment

7.9.5 **Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.**

AbbVie believes that the extensive subgroup analyses considered in this submission cover the most important patient subgroups affected by chronic hepatitis C.

7.10 Interpretation of economic evidence

7.10.1 **Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?**

There are no published economic models exploring the cost-effectiveness of AbbVie's regimen in chronic hepatitis C patients (GT1 or GT4). However, as described in section 7.8 of the submission, our model compares favourably to other published economic evaluations identified in the literature. The model is structurally based on the Hartwell et al. (2011) and Shepherd et al. (2007) models, and is well aligned with Wright et al. (2006), the original source of the majority of the input parameter to model chronic HCV disease progression. Based on these supportive facts, AbbVie considers that the results predicted by its cost-effectiveness model are credible.

7.10.2 **Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?**

The economic evaluation is relevant to all groups of patients identified in the decision problem. These groups were extensively studied across 9 AbbVie clinical trials, comprising over 2000 patients in totality and are all covered by AbbVie's regimen marketing authorisation.

7.10.3 **What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?**

Strengths

- SVR rates in AbbVie's trials have been reported according to the stage of liver disease (unlike for the competitor therapies) allowing for the model health states to be populated accordingly.

- Economic model has been developed in line with previously published models, using similar input parameters to model disease progression and health state utilities; this has ensured consistency with previous assessments and facilitates the ease of comparisons and validations of the model results.

- The economic model contains three recovered health states representing virologic cure of chronic HCV which are differentiated by the patients' stage of liver disease prior to treatment; this stratification facilitates modelling of the subsequent risk of progressive liver disease (important for recovered patients with history of CC).

Limitations

- It has not been possible to model the cost effectiveness of treatment of post liver transplant patients as the natural history, costs and utilities are not well characterised at present. However, it is anticipated that due to the high SVR rates and the poor prognosis of these patients, treatment with AbbVie 3D or 2D regimens for GT1 and GT4 respectively is likely to be more cost effective than the other subgroups modelled in the current analyses.

- SVR data are not available for cirrhotic GT4 patients therefore only non-cirrhotic GT4 patients have been modelled.

- There is very limited information on the baseline characteristics of patients suffering with chronic HCV in the UK; we found no information on the baseline characteristics for patients in the relevant subgroups and have used baseline characteristics from the overall treatment naïve and treatment experienced GT1patients; clinical experts however regarded these assumptions as reasonable and in line with their clinical experience; similar assumptions have been made in other NICE assessments in chronic HCV, namely the appraisals of sofosbuvir and simeprevir.[19,20]

- Health state utilities for the progressive liver health states (mild/moderate/CC/DCC/HCC/LT) were taken from the report (Wright et al 2006) on a multicenter trial in the UK, supplemented by the cohort and observational studies recruiting patients with compensated and decompensated cirrhosis; it is unclear how applicable these QoL weights are to some subgroups of patients in the current assessment; AbbVie however tested these values in extensive scenario analyses.

- There are numerous trials of peginterferon-ribavirin (PR) documenting SVRs in GT1 patients, published over a number of years. Originally, our intention was to model efficacy inputs using estimates from a mixed treatment comparison (MTC) for all products. However as a MTC was not feasible in this disease area, PR SVR estimates for treatment naïve and treatment experienced patients in our model base case are based on the SVRs of patients receiving PR in the ADVANCE and REALIZE trials respectively. We realise that this may be deemed a limitation of our modelling, however we explore this in scenario analyses where we apply alternative PR SVR rates.

- The scenario where 80% of treatment-naïve cirrhotic patients treated with SOF+ PR will be treated for 24 weeks, while 20% are treated for 12 weeks is limited due to the absence of clinical data. We thus do not vary SVR rates, AE rates, completion rates and on-treatment disutility between patients treated with 12 vs 24 weeks of SOF + PR. In this scenario, we vary: 1. regimen duration (and thus total cost of regimen); and 2. monitoring costs

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

- Better understanding of the natural history of disease for GT4 patients, SVR for GT4 cirrhotic patients and the natural history of post-transplant patients.

- The anecdotal evidence suggest that the achievement of SVR has the ability to regress the pathology of liver fibrosis, however long-term follow-up epidemiologic studies would be welcomed to establish whether this may be the case.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Public Health England (PHE), formerly the Health Protection Agency (HPA) maintains a Bayesian model to estimate the general HCV prevalence in England and Wales. The prevalence of anti-HCV antibody is thus estimated to be 0.4% amongst the adult population in England. We apply this prevalence to the adult population (18+) of England and Wales to estimate HCV antibody prevalent cases in England and Wales. A rate of 66% is further applied to adjust for viremia. There are six defined genotypes of HCV, with genotype 1 (GT1) being the most predominant in the UK accounting for 45% of the total chronic HCV infections and least responsive to treatment with PegIFN-RBV (PR)-based regimens. According to Harris et al (2000) we further assume that GT1a accounts for 66.8% of the overall GT1 patients. GT4 patients are assumed to account for 2% of all chronic HCV infections. In the UK, only approximately 3% of chronically infected patients are treated each year.

Patients infected with chronic genotype 1 HCV are eligible to receive 3D+/-RBV whereas patients infected with GT4 chronic hepatitis C are eligible to receive 2D+RBV. Therapeutic indications have been described in detail in Section 1.5 of the submission. Using population projections reported by the Office of National Statistics (ONS)[129], below we estimate the adult patient population eligible to receive therapy with either 3D or 2D.

Table 153: Estimates of the patient numbers eligible for treatment in England and Wales

	Epidemiology	2015	2016	2017	2018	2019
Adult population of England and Wales (18+)*		45,432,100	45,745,582	46,061,226	46,379,049	46,699,064
Estimated prevalence of chronic Hep C in adult population	0.40%	181,728	182,982	184,245	185,516	186,796
HCV RNA positive	66%	119,941	120,768	121,602	122,441	123,286
GT1 chronic HCV	45%	53,973	54,346	54,721	55,098	55,478
GT4 chronic HCV	2%	2,399	2,415	2,432	2,449	2,466
Proportion GT1 eligible for treatment	100%	53,973	54,346	54,721	55,098	55,478
Proportion GT4 eligible for treatment	100%	2,399	2,415	2,432	2,449	2,466
Proportion treated GT1 (6%-9%)**		3,238	3,261	3,830	4,408	4,993
Proportion treated GT4 (6%-9%)**		144	145	170	196	222
Proportion GT1 treatment-naïve treated	67%	2,170	145	2,566	2,953	3,345
Proportion GT1 treatment-experienced treated	33%	1,069	1,076	1,264	1,455	1,648

*ONS estimates that population of England and Wales will grow on average 0.7% year on year between 2013 and 2018. This growth rate has been used to estimate adult population growth between 2015 and 2020.
** Treatment rated anticipated to increase from 6% in 2015 to 9% in 2020 (see text).

Public Health England report states that as recently as 2012, only around 3% of chronically infected patients initiate treatment each year. Emerging data indicate that in the near future all-oral direct-acting antiviral (DAA) treatments for chronic HCV will become the first-choice therapy for a number of HCV-infected patients and will replace triple therapy approaches burdened with significant side-effects and limited success in patients with advance liver fibrosis and prior null-response to PegIFN/RBV. All-oral DAA regimens are expected to be more tolerable, more effective, shorter in duration and simpler to administer creating possibilities for more convenient and successful care. Assuming they are finally approved for use in the NHS England and Wales, the new interferon-free DAA regimens are likely to stimulate demand for therapy and in turn increase treatment rates. Increase in treatment rates may thus occur through 1) patients' desire to initiate IFN-free treatment, 2) treatment of patients who until now had to withhold therapy (IFN-ineligible or intolerant), and 3) greater clinician interest in treating patients as better outcomes are more likely to be achieved. We thus assume that between 2015 and 2019, treatment rate will increase from 6% in 2015 to 9% to 2019. Further, given the minor contribution of GT4 patients to the overall pool of persons infected with chronic hepatitis C in England, the budget impact of GT4 patients is not presented.

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

For both GT1 and GT4 patients, it is assumed that the ratio of treatment naïve to treatment experienced patients is 67% to 33%. This split is based on NICE's 'BOC and TPR for the treatment of genotype 1 chronic HCV costing template'[130] and is assumed not to vary across patient populations. In the first year, market shares of IFN-containing PI regimens are assumed to be approximately equal. However, over time, it is anticipated that their market shares would be displaced by the IFN-free regimens (please see section below).

8.3 What assumption(s) were made about market share (when relevant)?

Table 154 and Table 155 below detail the projected market share of therapies currently used to treat GT1, chronic HCV (Table 154) and their market share upon introduction of AbbVie's regimen in 2015 (Table 155). AbbVie assume that its regimen will gain 15% market share by the end of 2015. It further anticipates that 3D will continue to grow market share over 5 years (rising to 55% in 2019) with corresponding reductions occurring in the first generation PI regimens. A faster increase in market share for 3D than SOF+PR is anticipated given the increase in demand for IFN-free regimens.

Although not captured in our budget impact analysis, the projected market share for SOF+PR over the forecast period are likely to be displaced by the other regimens recently licensed but currently without NICE approval or those that have not yet received marketing authorisation but are anticipated to be licensed within the period of 2015 – 2019.

Table 154: Projected market share for current treatment options used to treat GT1, chronic hepatitis C patients

Regimen	2015	2016	2017	2018	2019
PR	12%	12%	10%	10%	5%
BOC+PR	20%	15%	15%	10%	10%
TPR+PR	32%	30%	25%	20%	20%
SOF+PR	36%	43%	50%	60%	65%

Table 155: Projected market share for current treatment options and 3D (following its marketing authorisation) used to treat GT1 chronic hepatitis C patients

Regimen	2015	2016	2017	2018	2019
PR	15%	12%	10%	7%	5%
BOC+PR	20%	15%	10%	5%	0%
TPR+PR	25%	20%	15%	8%	0%
SOF+PR	25%	25%	27%	35%	40%
3D	15%	28%	38%	45%	55%

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

There are no significant additional costs associated with AbbVie's regimens.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Detailed description of unit costs assumed for treatment and monitoring can be found in Section 7.5 of the submission.

8.6 Were there any estimates of resource savings? If so, what were they?

Shortened treatment duration and better tolerability profile of the AbbVie regimen over the PR based regimens is anticipated to render reductions of resource use associated with managing and monitoring of chronic HCV infection and treatment related side-effects. For details on 3D and comparators' AE rates, please refer to section 7.3 and for details around resource implications, please refer to section 7.5.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 156 and Table 157 below demonstrate the estimated budget impact for England and Wales for chronic, genotype 1 HCV patients based on the projected market shares of currently licensed therapies (Table 154) and the market share of therapies following the introduction of the 3D regimen to the market (Table 155). For the purpose of this budget impact analysis, we have only included annual per patient cost of treatments. Therefore, we have not accounted for the costs of AEs and monitoring costs associated with each treatment, which have discussed above and in sections 7.3 and 7.5 of the submission.

Assuming AbbVie 3D achieves a market share of 15% upon market entry in 2015, the estimated incremental budget impact to the NHS for treatment of chronic GT1 patients is £850,237. As the treatment rate increases from 6% in 2015 to 9% in 2019 and 3D achieves market share of 55%, the estimated incremental budget impact to the NHS increases to £26,477,045.

As mentioned in section 7.3, we have not been able to compare 3D with BOC+PR in GT1 treatment-experienced patients overall due to BOC+PR lacking data in null responder patients. However for the purpose of the budget impact analysis, we assume that the projected market share for BOC+PR are shared between treatment-naïve and treatment-experienced patients and further that the cost of treatment-experienced patients treated with BOC+PR is the same as the cost incurred by the treatment-naïve patients. However, due to longer treatment duration of treatment-experienced patients with BOC+PR, this is likely to be an underestimate of their total cost to the NHS.

No trials were conducted with sofosbuvir + PR in treatment-experienced, genotype 1 patients and therefore no cost-effectiveness analysis was possible between 3D and SOF+PR in treatment-experienced GT1, IFN-eligible patients. However, much like with the BOC+PR, we assume that GT1, IFN-eligible, treatment-experienced patients treated with SOF+PR will incur the same cost as treatment-naïve patients. This cost is thus used for the purpose of the budget impact analysis.

Table 156: Estimated annual budget impact for the NHS in England and Wales over 5 years based on the currently available therapies

Genotype 1, IFN-eligible patients	2015	2016	2017	2018	2019
Number of patients treated	3,238	3,261	3,830	4,408	4,993
PR market share	12%	12%	10%	10%	5%
Numbers treated with PR	389	391	383	441	250
PR treatment-naïve costs	£7,970	£7,970	£7,970	£7,970	£7,970
PR treatment-experienced patients costs	£7,046	£7,046	£7,046	£7,046	£7,046
Total Cost PR	**£2,978,711**	**£2,999,265**	**£2,936,072**	**£3,378,664**	**£1,913,612**
BOC+PR market share	20%	15%	15%	10%	10%
Numbers treated with BOC+PR	518	489	575	441	499
BOC+PR treatment-naïve costs	£19,739	£19,739	£19,739	£19,739	£19,739
BOC+PR treatment-experienced costs*	£19,739	£19,739	£19,739	£19,739	£19,739
Total Cost BOC+PR	**£12,784,556**	**£9,654,577**	**£11,341,393**	**£8,700,684**	**£9,855,809**
TPR+PR market share	32%	30%	25%	20%	20%
Numbers treated with TPR+PR	1,036	978	958	882	999
TPR+PR treatment-naïve costs	£25,499	£25,499	£25,499	£25,499	£25,499
TPR+PR treatment-experienced costs	£26,487	£26,487	£26,487	£26,487	£26,487
Total costs TPR+PR	**£26,762,180**	**£25,262,661**	**£24,730,391**	**£22,766,657**	**£25,789,215**
SOF+PR market share	36%	43%	50%	60%	65%
Numbers treated with SOF+PR	1,295	1,402	1,915	2,645	3,245
SOF+PR treatment-naïve costs	£37,133	£37,133	£37,133	£37,133	£37,133
SOF+PR treatment-experienced costs*	£37,133	£37,133	£37,133	£37,133	£37,133

Total costs SOF+PR	**£43,290,544**	**£52,064,936**	**£71,118,079**	**£98,206,346**	**£120,514,838**
Total estimated annual budget impact for the NHS	**£85,815,991**	**£89,981,439**	**£110,125,934**	**£133,052,350**	**£158,073,473**

*The cost of BOC+PR and SOF+PR in treatment-experienced GT1 patients is assumed to be the same as the cost for treating GT1 treatment-naïve patients

Table 157: Estimated future annual budget impact for the NHS in England and Wales over 5 years including 3D regimen

Genotype 1, IFN-eligible patients	2015	2016	2017	2018	2019
Number of adult patients treated	3,238	3,261	3,830	4,408	4,993
PR market share	15%	12%	10%	7%	5%
Numbers treated with PR	486	391	383	309	250
PR treatment-naïve costs	£7,970	£7,970	£7,970	£7,970	£7,970
PR treatment-experienced patients costs	£7,046	£7,046	£7,046	£7,046	£7,046
Total Cost PR	**£3,723,389**	**£2,999,265**	**£2,936,072**	**£2,365,065**	**£1,913,612**
BOC+PR market share	20%	15%	10%	5%	0%
Numbers treated with BOC+PR	648	489	383	220	0
BOC+PR treatment-naïve costs	£19,739	£19,739	£19,739	£19,739	£19,739
BOC+PR treatment-experienced costs*	£19,739	£19,739	£19,739	£19,739	£19,739
Total Cost BOC+PR	**£12,784,556**	**£9,654,577**	**£7,560,928**	**£4,350,342**	**£0**
TPR+PR market share	25%	20%	15%	8%	0%
Numbers treated with TPR+PR	810	652	575	353	0
TPR+PR treatment-naïve costs	£25,499	£25,499	£25,499	£25,499	£25,499
TPR+PR treatment-experienced costs	£26,487	£26,487	£26,487	£26,487	£26,487
Total costs TPR+PR	**£20,907,953**	**£16,841,774**	**£14,838,235**	**£9,106,663**	**£0**
SOF+PR market share	25%	25%	27%	35%	40%
Numbers treated with SOF+PR	810	815	1,034	1,543	1,997
SOF+PR treatment-naïve costs	£37,133	£37,133	£37,133	£37,133	£37,133
SOF+PR treatment-experienced costs*	£37,133	£37,133	£37,133	£37,133	£37,133

Total costs SOF+PR	**£30,062,878**	**£30,270,312**	**£38,403,763**	**£57,287,035**	**£74,162,977**
3D market share	15%	28%	38%	45%	55%
Numbers treated with 3D	486	913	1456	1984	2746
3D treatment-naïve costs	£37,770	£37,770	£37,770	£37,770	£37,770
3D treatment-experienced costs	£43,012	£43,012	£43,012	£43,012	£43,012
Total costs 3D	**£19,187,453**	**£36,063,712**	**£57,494,874**	**£78,349,519**	**£108,473,929**
Total estimated annual budget impact for the NHS	**£86,666,229**	**£95,829,640**	**£121,233,872**	**£151,458,623**	**£184,550,518**

*Cost of BOC+PR and SOF+PR in GT1 treatment-experienced patients is assumed to be the same as the cost for treating GT1 treatment-naïve patients

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

N/A.

9 References

[1] Draft summary of product characteristics (SPC), submitted May 2014. Revised October 2014.

[2] Charlton M. Hepatitis C infection in liver transplantation. *Am J Transplant*, 2001. **1**(3):197-203.

[3] Zaltron S, Spinetti A, Biasi L, Baiguera C, Castelli F. Chronic HCV infection: epidemiological and clinical relevance. *BMC Infect Dis* 2012;**12** Suppl 2:S2.

[4] Chen S, Morgan T. The natural history of hepatitis C virus (HCV) infection. *International Journal of Medcial Sciences* 2006; **3**(2):47-52.

[5] de Oliveria Andrade LJ, D'Oliveira A, Melo RC, De Souza EC, Costa Silva CA, Parana R. Association between hepatitis C and hepatocellular carcinoma. *J Glob Infect Dis* 2009;**1**:33-37.

[6] Lee MH, Yang HI, Lu SN et al. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis* 2012; **206**:469-477.

[7] Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology* 1998;**27**:209-212.

[8] Akobeng AK, Davison S. Quality of life of patients with chronic hepatitis C virus infection. *J Pediatr Gastroenterol Nutr* 2000;**30**:224-226.

[9] Zacks S, Beavers K, Theodore D, Dougherty L BBSJ, et al. Social stigmatization and hepatitis C virus. *J Clin Gastroenterol* 2006;40:220-224.

[10] Public Health England. Hepatitis C in the UK. *2014 report*, updated July 2014.

[11] Public Health England. Hepatitis C in the UK. *2013 report* 2013.

[12] Poynard T, Yuen MF, Ratziu V, Lai CL. Viral hepatitis C. *Lancet* 2003;**362**:2095-2100.

[13] National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance TA 200. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. September. 2010.

[14] Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2011;9:923-930.

[15] van der Meer AJ, Veldt BJ, Feld JJ et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012;**308**:2584-2593.

[16] van der Meer AJ, Veldt BJ, Feld JJ et al. The number needed to treat to prevent mortality and cirrhosis-related complications among patients with cirrhosis and HCV genotype 1 infection. *J Viral Hepat* 2013.

[17] Neal KR, Ramsay S, Thomson BJ, Irving WL. Excess mortality rates in a cohort of patients infected with the hepatitis C virus: a prospective study. *Gut* 2007;**56**:1098-1104.

[18] NICE Public Health Guidance No PH43. Hepatitis B and C: ways to promote and offer testing to people at risk of infection. March. 2013.

[19] National Institute for Health and Care Excellence. http://www.nice.org.uk/Guidance/InDevelopment/GID-TAG455/Documents. Accessed September 2014.

[20] National Institute for Health and Care Excellence. http://www.nice.org.uk/guidance/indevelopment/GID-TAG445. Accessed September 2014.

[21] European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatitis C virus infection. J Hepatol. 60, 392-420. 2014.

[22] North CS, Hong BA, Adewuyi SA et al. Hepatitis C treatment and SVR: the gap between clinical trials and real-world treatment aspirations. *Gen Hosp Psychiatry* 2013;**35**:122-128.

[23] Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern Med* 2002;**136**:288-292.

[24] National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance TA 253. Boceprevir for the treatment of genotype 1 chronic hepatitis C. 2012. Accessed September 2014.

[25] National Institute for Health and Clinical Excellence. NICE technology appraisal guidance 252 - Telaprevir for the treatment of genotype 1 chronic hepatitis C. April 2012. Accessed September 2014.

[26] Wyles DL. Beyond telaprevir and boceprevir: resistance and new agents for hepatitis C virus infection. *Top Antivir Med* 2012;20:139-145.

[27] Kiser JJ, Burton JR, Anderson PL, Everson GT. Review and management of drug interactions with boceprevir and telaprevir. *Hepatology* 2012;**55**:1620-1628.

[28] Lawitz E, Sulkowski M, Ghalib R, Rodriguez-Torres M, Younossi Z. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment naïve patients: the COSMOS randomised study. *Lancet* 2014. Published online July 28, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61036-9.

[29] Martin NK, Foster GR, Vilar J, Ryder S, E Cramp M, Gordon F, Dillon JF, Craine N, Busse H, Clements A, Hutchinson SJ, Ustianowski A, Ramsay M, Goldberg DJ, Irving W, Hope V, De Angelis D, Lyons M, Vickerman P, Hickman M. HCV treatment

rates and sustained viral response among people who inject drugs in seven UK sites: real world results and modelling of treatment impact. J Viral Hepat. 2014 Oct 7. doi: 10.1111/jvh.12338. [Epub ahead of print]

[30] Flemming JA et al. Increased rates of liver transplant wait-listing for hepatocellular carcinoma in individuals with hepatitis C from 2003-2010 in the United States. 64th Annual Meeting of the American Association for the Study of Liver Diseases, Washington, DC, abstract 12, 2013.

[31] Feld J, Kowdley K, Coakley E, Sigal S, Nelson D, Crawford D et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *NEJM* 2014. DOI: 10.1056/NEJMoa1315722.

[32] Zeuzem S, Jacobson I, Baykal T, Marinho R, Poordad F, Bourliere M. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *NEJM* 2014;**370**:1604-14.

[33] Poordad F, Hezode C, Trinh R, Kowdley K, Zeuzem S, Agarwal K. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *NEJM* 2014. DOI: 10.1056/NEJMoa1402869.

[34] Andreone P, Colombo M, Enejosa J, Koksal I, Ferenci P, Maieron A. ABt-450/r-ombitasvir and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment experienced patients with HCV genotype 1b infection. *Gastroenterology* 2014;**147**:359-365.

[35] Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin. *NEJM* 2014. DOI: 10.1056/NEJMoa1402338.

[36] Kowdley K, Lawitz E, Poordad F, Cohen D, Nelson D, Zeuzem S. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *NEJM* 2014;**370**(3):222-232.

[37] Integrated Summary of Efficacy (ISE). AbbVie data submission to EMA. 2014.

[38] Hezode C, Marcellin P, Pol S, Hassanein T, Fleischer, Stepniewska K et al. Results from the phase II PEARL-I study: Interferon-free regimens of ABT-450/r + ABT-267 with or without ribavirin in patients with HCV genotype 4. *Journal of Hepatology*, suppl. 1 60.1 (Apr 2014): S24.

[39] M13-393 Clinical Study Report (CSR) R&D/14/0577 - a Randomised, Open-Label Study to Evaluate the Safety and Efficacy of 2D in Adults with Chronic Hepatitis C Virus Infection (PEARL-I). AbbVie data.

[40] Anderson R, Baran R, Dietz B, Kallwitz E, Erickson P, Revicki D. Development and initial psychometric evaluation of the hepatitis C virus-patient reported outcomes (HVC-PRO) instrument. *Qual Life Res* 2014.**23**:561-570.

[41] Anderson R, Baran R, Erickson P, Revicki D. Dietz B, Gooch K. Psychometric evaluation of the hepatitis C virus-patient reported outcomes (HVC-PRO) instrument:

validity, responsiveness, identification of the minimally important difference in a phase II clinical trial. *Qual Life Res* 2014.**23**:877-886.

[42] M11-646 Clinical Study Report (CSR) R&D/13/353 – a randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of 3D with RBV in treatment naïve adults with genotype-1 hepatitis C virus (HCV) infection (SAPPHIRE-I). AbbVie data.

[43] M13-098 Clinical Study Report (CSR) R&D/13/354 – a randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of 3D with RBV in treatment-experienced adults with genotype-1 hepatitis C virus (HCV) infection (SAPPHIRE-II). AbbVie data.

[44] M13-099 Clinical Study Report (CSR) R&D/13/359. A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of 3D Co-administered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II). AbbVie data.

[45] M13-389 Clinical Study Report (CSR) R&D/13/358. A Randomized, Open-Label, Multicentre Study to Evaluate the Safety and Antiviral Activity of 3D With and Without Ribavirin in Treatment-Experienced Subjects with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection (PEARL–II) AbbVie data.

[46] M13-961 Clinical Study Report (CSR) R&D/13/355. A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of 3D With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection (PEARL-III). AbbVie data.

[47] M14-002 Clinical Study Report (CSR) R&D/13/356. A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of 3D With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1a Chronic Hepatitis C Virus (HCV) Infection (PEARL-IV). AbbVie data.

[48] Wallace B, Schmid C, Lau J, Trikalinos T. Meta-Analyst: software for meta-analysis of binary, continuouse and diagnostic data. BMC Medical Research Methodology 2009; **9**:80.

[49] M14-103 Clinical Study Report (CSR) R&D/13/360. An Open-label, Single-Arm, Phase 2 Study to Evaluate the Combination of 3D Co-administered with Ribavirin (RBV) in Adults with Genotype 1 Hepatitis C Virus (HCV) Infection taking Methadone or Buprenorphine. AbbVie data.

[50] Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**:1867–1877.

[51] Hartwell et al. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. Southampton Health Technology Assessments Centre (SHTAC), University of Southampton, Southampton, UK. *Health Technology Assessment* 2011;15(17).

[52] Blazquez-Perez A, San Miguel R, Mar J. Cost-effectiveness analysis of triple therapy with protease inhibitors in treatment-naive hepatitis C patients. *Pharmacoeconomics.* 2013;**31**(10):919-31.

[53] Townsend R, McEwan P, Kim R, Yuan Y. Structural frameworks and key model parameters in cost-effectiveness analyses for current and future treatments of chronic hepatitis C. *Value Health.* 2011;**14**(8):1068-77.

[54] Camma C, Petta S, Cabibbo G, Ruggeri M, Enea M, Bruno R, et al. Cost-effectiveness of boceprevir or telaprevir for previously treated patients with genotype 1 chronic hepatitis C. *J Hepatol.* 2013;59(4):658-66.

[55] Camma C, Petta S, Enea M, Bruno R, Bronte F, Capursi V, et al. Cost-effectiveness of boceprevir or telaprevir for untreated patients with genotype 1 chronic hepatitis C. *Hepatology* 2012 p. 850-60.

[56] Cure S, Bianic F, Gavart S, Curtis S, Lee S, Dusheiko G. Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in treatment-experienced chronic hepatitis C genotype 1 patients. *Journal of Medical Economics* 2014. p. 77-87

[57] Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa and ribavirin for chornic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technology Assessment (Winchester, England*). 2007;**11**(11):1-205.

[58] Elbasha EH, Chhatwal J, Ferrante SA, El Khoury AC, Laires PA. Cost-effectiveness analysis of boceprevir for the treatment of chronic hepatitis C virus genotype 1 infection in Portugal. Applied Health Economics and Health Policy2013. p. 65-78.

[59] Hartwell D, Jones J, Baxter L, Shepherd J. Shortened peginterferon and ribavirin treatment for chronic hepatitis C. *International Journal of Technology Assessment in Health Care* 2012 p. 398-406.

[60] McEwan P, Kim R, Yuan Y. Assessing the cost utility of response-guided therapy in patients with chronic hepatitis C genotype 1 in the UK using the MONARCH model. *Applied Health Economics & Health Policy*. 2013;**11**(1):53-63.

[61] Turnes J, Romero-Gomez M, Planas R, Sola R, Garcia-Samaniego J, Diago M, et al. Pharmacoeconomic analysis of the treatment of chronic hepatitis C with peginterferon alfa-2a or peginterferon alfa-2b plus ribavirin in Spain. *Gastroenterol Hepatol.* 2013;**36**(9):555-64.

[62] Khattab et al. Management of hepatitis C virus genotype 4: Recommendations of An International Expert Panel. *Journal of Hepatology* 2011;**54**(6):1250-62.

[63] Antaki et al. The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. *Liver International* 2010;**30**(3):342-55.

[64] Sangiovanni et al. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. *Hepatology* 2006;**43**(6):1303-10.

[65] Fattovich et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology*. 1997;**112**(2):463-72.

[66] Grishchenko et al. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. *International Journal of Technology Assessment in Health Care* 2009;**25**(2):171-80.

[67] Liu et al. New Protease Inhibitors for the Treatment of Chronic Hepatitis C: A Cost-Effectiveness Analysis. *Annals of Internal Medicine* 2012;**156**(4):279-90

[68] Ryder SD. UK Guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults. On behalf of the *HCC management in the UK (HUG)* writing committee 2009.

Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. *Gut* 2003;52(Suppl III):iii1-iii8.

[69] Achkar et al. Undetected hepatocellular carcinoma: clinical features and outcome after liver transplantation. *Liver Transplantation and Surgery* 1998;**4**(6):477-82.

[70] Wright M, Grieve R, Roberts J, Main J, Thomas HC, UK Mild Hepatitis C Trial Investigators. Health benefits of antiviral thrapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006;**10**(21).

[71] Foster GR, Goldin RD, Main J, Murray-Lyon I, Hargreaves S and Thomas HC. Management of chronic hepatitis C: clinical audit of biopsy based management algorithm. *BMJ* 1997;**315**:453-8.

[72] Harris, Kathryn Ann, et al. The most prevalent hepatitis C virus genotypes in England and Wales are 3a and 1a. *Journal of medical virology* 1999;**58**.2: 127-131.

[73] Pearlman BL and Traub N. Sustained Virologic Response to Antiviral Therapy for Chronic Hepatitis C Virus Infection: A Cure and So Much More. *Clinical Infectious Disease* 2011;**52**(7):889-900.

[74] Veldt et al. Long term clinical outcome of chronic hepatitis C patients with sustained virological response to interferon monotherapy. *Gut* 2004;**53**(10):1504-8

[75] Morisco et al. Sustained Virologic response: a milestone in the treatment of chronic hepatitis C. *World Journal of Gastroenterology* 2013;**19**(18):2793-8.

[76] Papastergiou et al. Durability of a sustained virological response, late clinical sequelae, and long-term changes in aspartate aminotransferase to the platelet ratio index after successful treatment with peginterferon/ribavirin for chronic hepatitis C: a prospective study. *European Journal of Gastroenterology and Hepatology* 2013;**25**(7):798-805.

[77] Koh et al. Long-term outcome of chronic hepatitis C after sustained virological response to interferon-based therapy. *Alimentary Pharmacology and Therapeutics* 2013;**37**(9):887-94

[78] Veldt et al. Long term clinical outcome of chronic hepatitis C patients with sustained virological response to interferon monotherapy. *Gut* 2004;**53**(10):1504-8

[79] Poynard et al. Impact of Pegylated Interferon Alfa-2b and Ribavirin on Liver Fibrosis in Patients With Chronic Hepatitis C. *Gastroenterology* 2002;**122**(5):1303-13.

[80] Aleman et al. A risk for hepatocellular carcinoma persists long term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. *Clinical Infectious Disease* 2013**;57**(2):230-6.

[81] Bruno et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 2007;**45**(3):579-87.

[82] Cardoso et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: Incidence and survival in hepatitis C patients with advanced fibrosis. *Journal of Hepatology* 2010;**52**:652-657.

[83] Salomon et al. Cost-effectiveness of Treatment for Chronic Hepatitis C Infection in an Evolving Patient Population. *JAMA* 2003;**290**(2):228-37.

[84] Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection. N Engl J Med. 2013;**368**:1878-1887.

[85] Jacobson et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. *N Engl J Med.* 2011;**364**:2405-2416.

[86] Kauffman RS et al., 2011. Review Activity/Safety: Telaprevir in Combination with Peginterferon Alfa-2A and Ribavirin Increased Sustained Virologic Response in Genotype 1 Chronic HCV. Conference Reports for NATAP. *Hep DART* 2011. available from
http://www.natap.org/2011/hepDART/hepDART_03.htm

[87] McHutchinson et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med*. 2009;**361**(6):580-93.

[88] Hadziyannis et al. Peginterferon-α2a and Ribavirin Combination Therapy in Chronic Hepatitis C: A Randomized Study of Treatment Duration and Ribarivin Dose. *Ann Intern Med*. 2004;**140**(5):346-55

[89] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol.* 2011;**55**:245-264.

[90] Poordad et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection. *N Engl J Med*. 2011;364:1195-1206.

[91] Zeuzem et al. Telaprevir for Retreatment of HCV Infection. *N Engl J Med*. 2011; **364**:2417-2428.

[92] CHMP Assessment Report: Incivo Procedure No.: EMEA/H/C/002313 European Medicines Agency Jul 2011.

[93] Kauffman RS, Muir AJ, Nelson DR, et al. Review Activity/Safety: Telaprevir in Combination with Peg-IFN-2A and Ribavirin Increased Sustained Virologic Response in GT1 Chronic HCV. Conference Reports for NATAP. *Hep DART* 2011. Web.

[94] Bacon et al. Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection. *N Engl J Med*. 2011;364:1207-1217.

[95] NICE sofosbuvir Single Technology Assessment (STA) chronic hepatitis C 2014; [ID654].

[96] Khattab MA, Ferenci P, Hadziyannis SJ, et al. Management of hepatitis C virus genotype 4: recommendations of an international expert panel. *J Hepatol* 2011;**54**(6):1250-62.

[97] Aljumah AA, Murad MH. Pegylated versus standard interferon plus ribavirin in chronic hepatitis C genotype 4: A systematic review and meta-analysis. *Hepatol Res* 2013;**43**(12):1255–63.

[98] Kamal SM, Ahmed A, Mahmoud S, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. *Liver Int*. 2011 Mar;**31**(3):401-11.

[99] Gamal Shiha and Khaled Zalata (2011). Ishak versus METAVIR: Terminology, Convertibility and Correlation with Laboratory Changes in Chronic Hepatitis C, Liver Biopsy, Dr Hirokazu Takahashi (Ed.), ISBN: 978-953-307-644-7, InTech, DOI: 10.5772/20110.

[100] Yee BE, Nguyen NH, Zhang B, et al. Meta-analysis: influence of host and viral factors in patients with chronic hepatitis C genotype 4 treated with pegylated interferon and ribavirin. *Eur J Gastroenterol Hepatol*. 2014;**26**(11):1189-201.

[101] Poynard T, Colombo M, Bruix J et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. *Gastroenterology*. 2009;**136**(5):1618-28.e2.

[102] Brady B, Siebert U, Sroczynski G, et al. Pegylated Interferon Combined with Ribavirin for Chronic Hepatitis C Virus Infection: An Economic Evaluation. *Technology Report No 82*. Ottawa: Canadian Agency for Drugs and Technologies in Health. 2007

[103] Jones J, Hartwell, D, Baxter L, Harris P. Telaprevir for the treatment of genotype 1 chronic hepatitis C. *Evidence Review Group Report* commissioned by the NHS R&D HTA Programme on behalf of NICE. 2011.

[104] NICE Simeprevir Single Technology Assessment (STA) chronic hepatitis C, 2014 [ID668].

[105] Grieve R, Roberts J, Wright M, et al. Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. *Gut.* 2006;**55**(9):1332-8

[106] Backx M, Lewszuk A, White JR, et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do not achieve sustained virological response to therapy. *Journal of viral hepatitis*. 2014; **21:**208-215.

[107] Thorlund K, Druyts E, El Khoury AC, Mills EJ. Budget impact analysis of boceprevir and telaprevir for the treatment of hepatitis C genotype 1 infection. *ClinicoEconomics and Outcomes Research*. 2012; **4**:349-359.

[108] AbbVie Data on File. Analysis of EQ-5D-5L data from AbbVie's pivotal trials.

[109] Younossi et al. Estimating Health Status EQ-5D for Chronic Hepatitis C (CH-C) Patients Treated with Sofosbuvir Containing Regimens. EASL, London UK. 2014: April 9-13.

[110] NICE Telaprevir for the treatment of genotype 1 chronic hepatitis C; TA252.

[111] NICE Boceprevir for the treatment of genotype 1 chronic hepatitis C; TA253.

[112] Curtis L. Unit Costs of health and Social Care. Personal Social Services Research Unit. 2013

[113] Danoff A, Khan O, Wan DW, Hurst L., et al. Sexual Dysfunction is Highly Prevalent Among Men with Chronic Hepatitis C Virus Infection and Negatively Impacts Health-Related Quality of Life. *Am J of Gastroenterology.* 2006;**101**:1235-1243.

[114] Roger AJ(1), Jolley D, Thompson SC, Lanigan A, Crofts N. The impact of diagnosis of hepatitis C virus on quality of life. Hepatology. 1999 Nov;30(5):1299-301

[115] Zickmund S(1), Ho EY, Masuda M, Ippolito L, LaBrecque DR. "They treated me like a leper". Stigmatization and the quality of life of patients with hepatitis C. *J Gen Intern Med.* 2003 Oct;**18**(10):835-44.

[116] EuroQoL available from www.euroqol.org; http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html) Last accessed on the 31 Oct 2014.

[117] Arnold DT, Bentham LM, Jacob RP, Lilford RJ, Girling AJ. Should patients with abnormal liver function tests in primary care be tested for chronic viral hepatitis: cost minimisation analysis based on a comprehensively tested cohort. *BMC Fam Pract.* 2011;12:9

[118] Backx M, Lewszuk A, White JR, Cole J, Sreedharan A, van Sanden S, et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. *J Viral Hepat*. 2014;**21**(3):208-15.

[119] Foxton MR, Al-Freah MA, Portal AJ, Sizer E, Bernal W, Auzinger G, et al. Increased model for end-stage liver disease score at the time of liver transplant results in prolonged hospitalization and overall intensive care unit costs. *Liver Transpl*. 2010;**16**(5):668-77.

[120] Thorlund K, Druyts E, El Khoury AC, Mills EJ. Budget impact analysis of boceprevir and telaprevir for the treatment of hepatitis C genotype 1 infection. *ClinicoEconomics and Outcomes Research*. 2012;**4**(1):349-59.

[121] Patruni, Bhanu, and Ellen Nolte. A projection of the healthcare and economic burden in the UK." *RAND Technical Report, prepared for the Hepatitis C Trust.* 2013.

[122] Vera-Llonch M, Martin M, Aggarwal J, et al. Health-related quality of life in genotype 1 treatment-naïve chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. *Alimentary Pharmacology & Therapeutics*. 2013;**38**(2):124–133.

[123] Briggs, Andrew H., A. E. Ades, and Martin J. Price. "Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework." Medical Decision Making 23.4 (2003): 341-350.

[124] Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001;**34**:809–16.

[125] Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin Liver Dis* 2000;**20**(1):17-35.

[126] Seeff LB. The history of the "natural history" of hepatitis C (1968-2009). *Liver Int*. 2009 Jan;29 Suppl 1:89-99.

[127] Thein HH, Yo Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008; **48**: 418–38.

[128] Brady B, Siebert U, Sroczynski G, Murphy G, Husereau D, Sherman M, Wong W, Mensinkai S. Pegylated interferon combined with ribavirin for chronic hepatitis C virus infection: an economic evaluation [Technology report no 82]. Ottawa: *Canadian Agency for Drugs and Technologies in Health*; 2007.

[129] ONS mid-2013 population projections available from: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/stb---mid-2013-uk-population-estimates.html Last accessed 10 Dec 2014.

[130] Boceprevir and telaprevir NICE costing template, available from: http://www.nice.org.uk/guidance/TA252/resources Last accessed 10 Dec 2014.