NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Sofosbuvir – Chronic hepatitis C

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Abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	Adverse Event
AFP	Alfa-fetoprotein
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AoD	Alcohol and other Drugs
APRI	AST: platelet ratio index
AST	Aspartate transaminase
AUD	Australian Dollars
BC	Base Case
BDI	Beck Depression Inventory
BID	Twice A Day
BIM	Budget Impact Model
BMI	Body Mass Index
BNF	British National Formulary
BOC	Boceprevir
CAD	Canadian Dollars
CEA	Cost Effectiveness Analysis
CES-D	Centre for Epidemiologic Studies Depression Scale
CFS	Cancer Fatigue Scale
CHC	Chronic Hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CLDQ-HCV	Chronic Liver Disease Questionnaire – Hepatitis C Virus
CLDQ-I	Chronic Liver Disease Questionnaire Instrument
CLT	Cadaveric Liver Transplantation
CMA	Cost Minimisation Analysis
CNS	Central Nervous System
CRD	Centre for Review and Dissemination
CUA	Cost Utility Analysis
DARE	Database of Abstracts of Reviews of Effects
DIC	Deviance Information Criterion
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	EuroQol-5 Dimensions
EOTR	End of Treatment Response
ER	Emergency Room
ERG	Evidence Review Group
EVR	Early Virological Response
eRVR	Extended rapid virological response
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FAS	Final Analysis Set
FBC	Full Blood Count
FDA	Food and Drugs Administration
FIS-D	Fatigue Impact Scale - Daily
GBP	Great British Pounds
GP	General Practitioner
GT	Genotype
HADS	Hospital Anxiety and Depression Scale
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCHS	Hospital and Community Health Service
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPA	Health Protection Agency
HR	Hazard Ratio
HRG	Health Related Group
HRQoL	Health Related Quality of Life
HRSD-21	Hamilton Rating Scale for Depression – 21 items
HTA	Health Technology Assessment
HUI	Health Utility Index
IBD	Inflammatory bowel disease
IBS	Inflammatory bowel syndrome
ICER	Incremental Cost Effectiveness Ratio
IDU	Intravenous Drug User
IFN	Interferon
INMB	Incremental Net Monetary Benefit
INR	International Normalised Ratio
KOL	Key Opinion Leaders

kPa	kiloPascal
LDLT	Living Donor Liver Transplantation
LFT	Liver Function Tests
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantitation
LT	Liver Transplant
LY	Life Years
MCS	Mental Health Component Scale
MEDLINE	Medical Literature Analysis and Retrieval System Online
MELD	Model of End-Stage Liver Disease
MOS - SF-36	Medical Outcome Study Short Form - 36
MRI	Magnetic resonance imaging
MSP	Multidisciplinary Support Program
MTC	Mixed Treatment Comparison
MUIS-A	Mishel's Uncertainty in Illness Scale
NHS	National Health Service
NHS-EED	National Health Service - Economic Evaluation Database
NICE	National Institute of Health and Care Excellence
NR	Not Reported
NT	No treatment
OD	Once Daily
ONS	Office of National Statistics
OR	Odds Ratio
PbR	Payment by Results
PCR	Polymerase Chain Reaction
PCS	Physical Component Summary
PEG-IFN	Pegylated interferon α
PEG-IFN-2a	Pegylated interferon α - 2a
PEG-IFB-2b	Pegylated interferon α – 2b
PI	Protease Inhibitor
PICO	Population, Intervention, Comparator, Outcome
PR	Pegylated interferon α - 2a and Ribavirin
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PR48	Pegylated interferon α - 2a and Ribavirin (Treatment Duration 48 weeks)
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTSS-10	Post-Traumatic Stress Syndrome 10-Questions Inventory
pTVR	Post-Transplant Virological Response

PubMed	Public MEDLINE
q8h	Every 8 Hours
QALY	Quality Adjusted Life Year
QoL	Quality of life
RBP	RibaPak
RBV	Ribavirin
RCT	Randomised Controlled Trial
RGT	Response Guided Therapy
RMSD	Root Mean Square Deviation
RNA	Ribonucleic acid
RPFS	Revised Piper Fatigue Scale
RVR	Rapid Virological Response
SAE	Serious Adverse Event
SAT-P	Satisfaction Profile
SCL90	Symptom Checklist-90
SD	Standard Deviation
SE	Standard Error
SF-12	Short Form -12 items
SF-36	Short Form - 36 items
SF-6D	Short Form - 6 Dimensions
SHTAC	Southampton Health Technology Assessments Centre
SKT	Short Cognitive Test
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SOF	Sofosbuvir
SmPC/IFU	Summary of Product Characteristics/Instructions For Use
STA	Single Technology Assessment
SVR	Sustained Virological Response
SVR4	Sustained Virological Response 4 weeks after the end of treatment
SVR12	Sustained Virological Response 12 weeks after the end of treatment
SVR24	Sustained Virological Response 24 weeks after the end of treatment
TE	Treatment-Experienced
TFT	Thyroid function tests
TID	Three Times a Day
TN	Treatment-naïve
TNF	Tumour Necrosis Factor
TP	Transition Probabilities
TPV	Telaprevir

TTO	Time Trade Off
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
USD	United States Dollars
WHOQOL-BREF	World Health Organization Quality of Life assessment instrument
weeks	weeks
WPAI	Work Productivity and Activity Impairment Questionnaire
WPQ	Work Productivity Questionnaire

Executive summary

Introduction

Burden of disease

Hepatitis C is associated with significant morbidity, mortality and economic burden. It is a progressive disease caused by the hepatitis C virus (HCV) which infects the liver. Acute infection is generally asymptomatic and between 15-25% of acutely affected individuals will gradually show a decrease in virus levels (Chen and Morgan 2006)[1]. The remaining 75-85 % go on to develop chronic HCV (CHC) and of these 5% and 25% will go on to develop cirrhosis over a 20-30 year period and be at risk of progression to decompensated cirrhosis and hepatocellular carcinoma (HCC) and therefore at risk of dying from liver related complications. In addition to the morbidity and mortality associated with liver-related disease, chronic HCV infection is associated with increased morbidity and mortality from extrahepatic diseases, including circulatory diseases, renal diseases, autoimmune disorders, cutaneous manifestations and non-liver cancers (Himoto and Masaku 2012, Lee *et al*. 2012)[2;3]. CHC is the most common cause of cirrhosis and the most common indication for liver transplantation in Europe (Zaltron *et al*. 2012)[4].

CHC also leads to impairment in quality of life (QoL) with patients feeling unwell in terms of both their physical and mental health (Foster *et al.* 1998, Akobeng and Davison 2000)[5;6] In addition to a reduced quality of life patients also have to manage with the social stigma associated with CHC (Zachs *et al*. 2006)[7].

CHC is associated with a considerable health burden with an estimated 215,000 individuals chronically infected with hepatitis C in the UK (Public Health England 2013)[8] including 160,000 people in England (Public Health England 2013)[8]. While levels of HCV infection are declining the prevalence of hepatitis C 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 (Public Health England 2013)[8]. 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 (Public Health England)[8].

Current treatment options and unmet need

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 (Poynard *et al.* 2003)[9]. 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. 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 (Ng *et al*. 2011, van der Meer *et al*. 2012, van der Meer *et al*. 2013)[10-12].

Currently two main treatment options provide the standard of care for patients with CHC:

- Protease inhibitors telaprevir and boceprevir in combination with peginterferon and ribavirin for patients with genotype GT1
- Peginterferon plus ribavirin (PEG-INF + RBV). Monotherapy PEG-IFN is recommended for patients who are unable to tolerate ribavirin or for whom RBV is contraindicated

While these current treatment options are successful and provide a cure for some patients they are not successful in a substantial proportion (EASL, 2014)[13]. 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 (Shah *et al*. 2013)[14].

The current standard of care treatment peginterferon plus ribavirin is also 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 (all genotypes) remain untreated due to contraindications to interferon therapy such as hepatic decompensation, autoimmune disease and psychiatric illness (Falck-Yteer Y *et al.* 2002)[15]. Treatment efficacy is influenced by genotype, stage of liver disease and the patient's prior treatment status. Given that re-treatment has a low chance of success, treatment-experienced patients represent an important group of patients that contribute to the unmet need in HCV, leaving such patients without treatment options and at risk of long term complications of HCV infection.

The limitations with current treatments 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. Of all diagnosed HCV patients, only 20% (approximately) actually commence treatment and only 3% to 4% of the total diagnosed population achieves a SVR (North *et al.* 2013)[16].

<u>Unmet need</u>

There is a clear medical need for new treatments which provide shorter, simpler, better tolerated and more effective pan genotypic regimens with a high likelihood of success. Those which have a high barrier to resistance and no drug to drug interactions and which can be used for the treatment of naïve and treatment experienced patients with CHC including those suitable to take interferon. Interferon-limiting and interferon-free treatment options can reduce or eliminate the limitations associated with long-term interferon use and avoid contraindications that would open up the possibility of cure to a broader population of patients.

The Technology – Sofosbuvir (SOF)

UK approved name: Sovaldi

Marketing status: CHMP positive opinion: 6th November 2013

Principal mechanism of action: Sofosbuvir is a first-in-class oral uridine nucleotide. It is a pan-genotypic inhibitor of the hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase which is essential for viral replication.

Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism within the hepatocytes to form a pharmacologically active uridine triphosphate which can be incorporated into the HCV RNA by the NS5B RNA-dependent RNA polymerase and cause chain termination during replication of the viral genome.

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

Film coated tablets containing 400 mg sofosbuvir are supplied in packs for 28 tablets. The acquisition cost for a 28 day pack is £11,660.98. The dose of sofosbuvir is 400 mg once a day. Repeated courses are not anticipated.

In comparison to current standards of care response-guided therapy is not required.

The indication: Sofosbuvir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

The recommended course of treatment: The average length of a course of treatment is 12 or 24 weeks according to genotype and status with regards to interferon (see below):

Average length of a course of treatment	12 or 24 weeks according to genotype and status with regards to interferon. For patients with GT1, 3 to 6 the standard regimen is sofosbuvir + ribavirin† + peginterferon alpha for 12 weeks or in patients unsuitable for interferon sofosbuvir+ribavirin for 24 weeks. For patients with GT2 the standard regimen is sofosbuvir + ribavirin12 weeks
Patients with (genotype) GT1,4,5 or 6 CHC	Sofosbuvir +ribavirin +peginterferon alpha 12 weeks
	Sofosbuvir ribavirin† 24 weeks (only for use in patients ineligible or intolerant to peginterferon alpha)
Patients with GT2 CHC	Sofosbuvir+ribavirin +12 weeks*
Patients with GT3 CHC	Sofosbuvir+ribavirin + peginterferon alpha 12 weeks*
	Sofosbuvir+ribavirin 24 weeks
Patients with CHC awaiting liver transplantation	Until liver transplantation. Duration should be guided by an assessment of the potential benefits and risks for the individual patient

*Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies e.g. advanced fibrosis/ cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peginterferon alpha and ribavirin therapy.

The main comparators are:

- Protease inhibitors - telaprevir or boceprevir, in combination with PEG-INF + RBV are recommended by NICE and are appropriate comparators for patients with GT1.
- PEG-INF and/or RBV
- No available treatment. For a significant proportion of patients there are no alternative treatment options (i.e. those unsuitable for inteferon – such as those who are medically ineligible, those who are interferon-intolerant or unwilling to take interferon). For such patients the alternative is a 'no treatment' or placebo comparator.

Summary key clinical evidence

Sofosbuvir has been studied in an extensive clinical trial programme covering all HCV genotypes (GT1–6), in a broad spectrum of patients representative of those seen in clinical practice. Patient populations studied included HCV treatment-naïve and treatment-experienced patients, those for whom current standard of care IFN-

based regimens are unsuitable, special populations such as those with HIV co-infection and pre-liver transplant, and those with characteristics that have historically been associated with poor response to treatment such as cirrhosis, older age, high BMI and high baseline HCV viral loads.

The key clinical evidence for sofosbuvir 400mg once a day supporting this submission comes from five pivotal Phase 3 studies:

- NEUTRINO (Lawitz *et al.* 2013a)[17] – a single group, open label randomised control study of SOF + PEG-IFN-2a + RBV in treatment naïve patients with HCV patients GT1, 4 , 5 or 6
- FISSION (Lawitz *et al.* 2013a)[17] – a open label, active control study comparing SOF + RBV for 12 weeks with PEG+RBV for 24 weeks in treatment naïve HCV patients GT 2 or 3
- FUSION (Jacobson *et al*. 2013a)[18] – a double-blind active controlled study comparing SOF + RBV for 12 weeks with SOF+RBV for 16 weeks in treatment experienced HCV patients GT 2 or 3
- POSITRON (Jacobson *et al*. 2013a)[18]– a double-blind, placebo controlled study comparing SOF + RBV for 12 weeks with placebo in patients unsuitable for IFN (e.g. IFN-intolerant, ineligible or unwilling)
- VALENCE (Interim CSR)[19] – a double-blind, placebo controlled study initially comparing SOF + RBV for 12 weeks with placebo in treatment-naïve, treatment-experienced and IFN-unable HCV GT2 or 3 patients. Based on emerging data from the FUSION trial VALENCE was unblended and all GT2 patients continued to received 12 weeks of SOF + RBV while patients who had not yet completed treatment were administered SOF + RBV for 24 weeks.

In each study the primary endpoint was the proportion of patients with a sustained virological response (SVR) 12 weeks after discontinuation of therapy.

In addition to the above pivotal phase 3 studies supportive information is provided by a detailed Phase 2 programme which includes (LONESTAR-2) a Phase 2 study evaluating the efficacy of a 12 week SOF + PEG-IFN-2a + RBV in treatment-experienced patients with GT2 and 3 including those with cirrhosis. Data is also available supporting the use of sofosbuvir in patients pre-liver transplantation and patients co-infected with HIV.

Main results of the randomised controlled trials

The results from the five Phase 3 trials show that treatment with SOF in combinations with PEG-IFN-2a and/or RBV results in rapid-on-treatment virological suppression and high cure rates across all HCV genotypes tested (SVR12 ≥ 90% in treatment-naïve patients and ≥ 77% in treatment experienced patients). High cure rates are also shown in patients with difficult-to-treat disease, such as those with cirrhosis and specific sub populations such as those with HIV and those awaiting liver transplantation.

Summary SVR12 results for each Phase 3 study are provided below. The high pan-genotypic potency of sofosbuvir is demonstrated by the rapidity of viral suppression, with almost all patients treated with sofosbuvir clearing HCV RNA by treatment Week 4. In the Phase 3 clinical development programme, all patients had cleared HCV RNA from the blood at the end of treatment. Where an SVR was not was achieved this was due to relapse after the end of therapy. Therefore, early viral kinetics are not predictive of response and a response guided therapy

approach is not necessary with sofosbuvir-based regimens, thereby simplifying patient monitoring and management compared with IFN-based regimens.

- NEUTRINO - Treatment-naïve patients HCV GT1, 4, 5 and 6 (Lawtiz *et al.* 2013a)[17]

  91% of patients treated with SOF + PEG-IFN-2a + RBV achieved an SVR12. This was superior to a historical response rate adjusted for cirrhosis and expected safety benefit (p<0.001).

  Response rate was unaffected by baseline variables other than the presence of cirrhosis or IL28B genotype; however SVR12 was ≥ 80% in all subgroups. The 81% SVR12 rate achieved in GT1 patients with compensated cirrhosis is the highest ever reported with any currently approved treatment regimen in this challenging patient group.

- FISSION – Treatment-naïve patients HCV GT2 or 3 (Lawtiz *et al.* 2013a)[17]

  In this study HCV treatment-naïve patients with GT2 or 3 had a SVR of 67% 12 weeks after the end of treatment with SOF + RBV (12 weeks treatment) which was non-inferior to PEG + RBV treatment (24 weeks), meeting the primary endpoint of non-inferiority vs. PEG + RBV (the current standard of care).

  Patients with HCV GT2 treated with SOF + RBV for 12 weeks achieved a very high rate of SVR12 (97% vs. 78% with PEG-IFN-2a + RBV). In GT3 patients, treatment with SOF + RBV for 12 weeks resulted in similar overall SVR12 rates to PEG-IFN-2a + RBV (56% and 63%, respectively).

  Significant between-treatment differences in favour of SOF+RBV versus PEG-IFN + RBV were observed in GT2 patients overall. SVR12 in GT2 was high irrespective of cirrhosis (98% in patients without cirrhosis vs. 91% in patients with cirrhosis for SOF + RBV; compared with 82% and 62% respectively with PEG-IFN-2a +RBV). SVR 12 in GT3 with patients with cirrhosis was similar between the treatment groups (34% SOF+RBV vs. 30% PEG-IFN-2a + RBV)

  The data from this study are consistent with the growing expert opinion that HCV GT2 patients have higher SVR rates than GT3 HCV patients to both interferon-containing and interferon-free regimens and should be considered as separate populations. Studies evaluating longer durations of SOF + RBV treatment to further increase response rates in GT3 patients include FUSION and VALENCE and are reported below.

- FUSION – Treatment experienced patients HCV GT2 or 3 (Jacobson *et al.* 2013a)[18]

  HCV patients with GT2/3 HCV infection who had failed on prior interferon treatment achieved SVR12 (a difficult to treat population who currently have limited treatment options) rates of 50% and 73%, with 12 weeks and 16 weeks of SOF + RBV treatment, respectively and met the primary endpoint of superiority over the historical control (p<0.001 for each comparison).

  Genotype was an important factor in determining SVR12 and the effect of extended treatment duration. In GT2 patients treated for 16 weeks resulted in a similar SVR12 rate to that achieved after 12 weeks of treatment (84% vs. 86% respectively). In GT3 patients the SVR12 rate was significantly higher after 16 weeks treatment and more than double that achieved following 12 weeks treatment (62% vs. 30% respectively)

In GT3 patients, compared with 12 weeks of treatment, 16 weeks of treatment with SOF + RBV improved SVR12 more than 3-fold (19% vs. 61%, respectively) in cirrhotic patients and almost 2-fold (37% vs. 63%, respectively) in patients without cirrhosis.

Following the results of the FUSION study it was postulated that an even longer duration of treatment may offer GT3 patients an improved chance of achieving SVR. This was assessed in the European Phase 3 VALENCE study reported below in which treatment duration in patients with GT3 infection was extended to 24 weeks .

- POSITRON – Patients unsuitable for interferon HCV GT2 or 3 (Jacobson *et al.* 2013a)[18]

  SVR12 was achieved by 78% of patients in the SOF + RBV group compared with 0% patients in the placebo group (p<0.001) and the primary endpoint of superiority over placebo was met.

  POSITRON included patients for whom IFN-based treatment was not an option and who currently have no treatment options and a high proportion of patients with negative predictors of response to IFN.

  Efficacy was significantly increased among patients with HCV GT2 infection compared with GT3. In patients with GT 2 SVR 12 was 94% in patients with cirrhosis and 92% in patients without cirrhosis. Presence of cirrhosis appeared to reduce the SVR12 response in GT3 patients. In total 91% and 61% of GT3 patients achieved SVR 12. SVR12 was 21% in patients with cirrhosis and 68% in patients without cirrhosis.

- VALENCE – Treatment naïve and experienced patients HCV GT2 or 3 (VALENCE Interim CSR)[19]

  In GT2 HCV-infected patients consistent with other studies, 12 weeks of treatment with SOF + RBV was associated with a high SVR12 rate (88 to 100%) irrespective of cirrhosis.

  In GT3 HCV-infected patients, SOF+RBV for 24 weeks resulted in an SVR12 of 85%; treatment-naïve patients achieved rates >90% irrespective of cirrhosis status. GT3 treatment-experienced patients achieved SVR12 rates of 85% and 60% respectively in the absence or presence of cirrhosis.

  Extending duration to 24 weeks improved response in GT3 patients and was as well tolerated as 12 weeks of therapy with no additional adverse events.

  These data clearly support the recommended duration of 24 weeks for all oral IFN-free therapy with SOF + RBV in those GT3 patients who are unsuitable for a 12 week IFN based regimen of SOF + PEG-INF + RBV.

Sofosbuvir has an excellent safety and tolerability profile with no adverse reactions specific to sofosbuvir identified.

Sofosbuvir is associated with low discontinuation rates from adverse events (≤ 2.4% in the five pivotal Phase 3 studies) and has a high barrier to the development of treatment resistant mutations which means that re-treatment of patients with sofosbuvir regimens is possible.

Pan-genotypic efficacy of sofosbuvir

The benefits of sofosbuvir across the different genotypes are as follows:

HCV GT1 treatment naïve patients

- In the pivotal phase 3 study NEUTRINO treatment with SOF + PEG-IFN-2a + RBV for 12 weeks resulted in high rates of sustained virologic response 12 weeks after the end of treatment (SVR12) in GT1 patients (sub-group analysis: 262/292 patients; 90%).

- The 81% SVR12 rate achieved in GT1 patients with compensated cirrhosis is the highest rate ever reported with any currently approved treatment regimen in this challenging sub-population.

- Treatment with SOF + PEG-IFN-2a + RBV for 12 weeks results in very high rates of SVR12 in both GT1a patients and GT1b patients, offering an effective and simple, well-tolerated regimen of short duration, without the need for response guided therapy.

- This regimen also resulted in high rates of SVR12 in other patient groups that have historically been associated with lower rates of response to treatment, including those with a high body mass index, a high baseline viral load, those of Black race or with a non-CC IL28B genotype.

- For treatment-naïve GT1 patients unsuitable for IFN-based therapy, treatment with all-oral SOF + RBV for 24 weeks offers a simple, effective, all-oral alternative regimen.

HCV GT1 treatment experienced patients

- The optimal treatment duration for treatment-experienced GT1 patients has currently not been established. As per the SmPC it is recommended that consideration should be given to treating these patients, and potentially extending the duration of therapy with SOF + PEG-IFN + RBV beyond 12 weeks and up to 24 weeks, especially for those patients who have one or more factors historically associated with lower response rates to IFN-based therapies.

HCV GT2 treatment naïve and treatment experienced patients

- In GT2 patients, treatment with all-oral SOF+RBV for 12 weeks resulted in very high rates of SVR12 irrespective of the presence of cirrhosis and prior treatment history

- Sofosbuvir offers the benefit of a simple, effective, all-oral (IFN-free) regimen with a shorter treatment duration compared with the current standard of care to all GT2 patients. This includes those who failed to respond to IFN-based therapy previously or those who are unable to be managed with IFN-containing regimens; patient groups that currently have limited or no treatment options and no standard of care.

- In treatment-naïve GT2 patients SOF + RBV for 12 weeks was significantly better than standard of care PEG-IFN-2a + RBV for 24 weeks in achieving SVR12 (FISSION Phase 3 sub-group analysis: 97% vs. 78%; between treatment difference, 19.5%, 95% CI 8.4%, 31.5%). Response rate in GT2 cirrhotic patients was also high for sofosbuvir (SVR12, 91%).

- In treatment-experienced GT2 patients (FUSION Phase 3; failed on previous IFN therapy) and GT2 patients who are unsuitable for IFN therapy (POSITRON, Phase 3), SVR12 rates with SOF + RBV for 12 weeks were 86% and 93%, respectively (sub-group analyses). SOF + RBV for 12 weeks provides a simple, all-oral (IFN-free) regimen in these patient groups which currently have limited or no treatment options.

HCV GT3 treatment-naïve and treatment experienced patients

- Historically patients with GT2 and GT3 infection have been grouped together as 'easier-to-treat' genotypes compared with others such as GT1. The pivotal Phase 3 sofosbuvir studies, FISSION, FUSION and POSITRON, took the same approach and studied SOF+RBV for 12 weeks in patients with HCV GT2/3 infection. The results demonstrated that GT3 is harder to treat than GT2 and are consistent with growing expert opinion that GT2 and GT3 HCV behave differently and should be considered separately in terms of treatment approach and how to be studies in future trials.
- The sofosbuvir licence considers GT3 as a distinct population and for treatment naïve, treatment experienced, cirrhotic and non-cirrhotic patients recommends 12 weeks of triple therapy with SOF+PEG-IFN+RBV or 24 weeks of treatment with SOF + RBV for those unsuitable for IFN.
- SOF + PEG-IFN + RBV for 12 weeks:
  - In treatment-naïve patients, sofosbuvir triple therapy resulted in SVR12 rates of 90% (PROTON, Phase 2) and 100% (ELECTRON, Phase 2). However patient numbers were small (GT3 patients: n=10 and 29, respectively).
  - In treatment-experienced GT3 patients, 12 weeks of sofosbuvir triple therapy (LONESTAR-2) resulted in SVR12 rate of 83% (sub-group analysis, n=24).
- SOF + RBV for 24 weeks:
  - In VALENCE (Phase 3) an SVR12 rate of 93% was achieved with SOF + RBV for 24 weeks in treatment-naïve GT3 patients (sub-group analysis). In treatment-experienced GT3 patients the same regimen resulted in an SVR12 rate of 77% (sub-group analysis). These populations included patients that were unsuitable for IFN, a population for which there are no treatment options.

HCV GT4, GT5 or GT6 patients

- Sofosbuvir (in combination with PEG-IFN + RBV for 12 weeks) is the only direct acting HCV antiviral agent to have been studied in these genotypes in Phase 3 trials to date and has resulted in high rates of SVR12 in GT4/5/6 patients (NEUTRINO Phase 3 sub-group analysis: 34/35 patients; 97%).. Although patient numbers, particularly for GT5 and GT6, are limited, this reflects the limited number of patients in the 'under treater care' population with these HCV genotypes

HIV co-infected patients

- For patients with HIV/HCV co-infection, a simple, IFN-free, all-oral regimen of sofosbuvir + RBV resulted in high SVR rates in HCV-treatment-naive patients with HCV GT 1, GT 2 and GT 3 infection that are similar to those seen in mono-infected patients.

HCV patients pre-liver tranplansplantation

- For liver transplant patients, all-oral SOF + RBV for ≤48 weeks prior to transplantation prevented HCV recurrence in the majority of patients, with 64% achieving post-transplant virological response compared to a near universal historical risk of reinfection in the absence of prophylaxis. On-treatment HCV RNA suppression in patients with well-compensated cirrhosis awaiting transplantation for HCC (liver cancer) was rapid and similar to other patient populations. SOF + RBV offers the first all-oral regimen for use across all genotypes for patients awaiting liver transplantation.

Type of economic evaluation and justification for the approach used

This submission assesses the cost-effectiveness of SOF in combination with RBV (with/without PEG-IFN) compared to PEG-IFN-2a + RBV, telaprevir + PEG-IFN-2a + RBV, boceprevir + PEG-IFN-2b + RBV and best supportive care within its licensed indication from the perspective of the NHS and PSS in England and Wales.

A Markov state-transition model was adapted from previous economic models developed by the Southampton Health Technology Assessment Centre (SHTAC) in the UK for NICE (Shepherd *et al.,* 2007 and Hartwell *et al*., 2011). The model structure was amended, according to the best data available from SOF phase III trials, to allow patients enter the model in non-cirrhotic (including mild and moderate CHC) or compensated cirrhosis health states. Patients who achieve SVR after treatment are considered to be virologically cured and those without achieving SVR may remain in their current health state or progress to more advanced stages of the disease (decompensated cirrhosis [DCC], HCC or liver transplant [LT]).

Cost effectiveness results

Sofosbuvir-based regimens offer a favourable cost-effectiveness profile compared with current standards of care. Across all HCV genotypes (GT 1-6), including patients with compensated cirrhosis, and irrespective of treatment experience or IFN eligibility, sofosbuvir is associated with overall QoL gains (QALYs), a greater probability of cure (SVR rates), and reduction in death rate.

The base case results are summarised in Table 1 to table 4 by indication, followed by incremental cost-effectiveness results (Table 5).

<u>GT 1</u>

For patients with GT1 infection, triple therapy with SOF + PEG-IFN-2a + RBV for 12 weeks offers a simple, efficacious, well-tolerated treatment which is cost-effective compared with PEG-IFN-2a + RBV, telaprevir + PEG-IFN-2a + RBV, boceprevir + PEG-IFN-2b + RBV (ICERs <£15,000/QALY). In addition, for those GT1 patients who are unsuitable for IFN-based therapy and currently have no treatment options available, SOF + RBV for 24 weeks offers the potential of a cure using an all oral, IFN-free regimen (ICER: £49,249/QALY).

<u>GT2</u>

SOF + RBV for 12 weeks is highly cost-effective (ICERs <£13,000/QALY) against current available comparators among GT2 patients who are treatment naïve (TN) or treatment experienced (TE) unsuitable for IFN and TE IFN eligible. For treating

GT2 TN IFN eligible patients, SOF + RBV has an estimated ICER of £46,324/QALY against PEG-IFN-2a + RBV. Despite this, sofosbuvir can potentially cure (SVR) 95% of these patients.

GT3

In GT3 patients, triple therapy with SOF + PEG-IFN-2a + RBV for 12 weeks offers a cost-effective option for the treatment of IFN eligible TN and TN patients (ICERs: <£22,000/QALY). In addition, for those GT3 patients who are unsuitable for IFN and currently have no treatment options available, an all oral, IFN-free regimen of SOF + RBV for 24 weeks offers the potential of a cure using a cost-effective IFN-free regimen (ICERs <£30,000/QALY).

GT4/5/6

The ICER for SOF + PEG-IFN-2a + RBV for 12 weeks compared with PEG-IFN-2a + RBV is estimated to be £26,797/QALY in patients with GT4/5/6 infection. This ICER is considered to be conservative since the SVR for sofosbuvir for cirrhotic patients (50%) is based on a small number of patients. The cure rate for non-cirrhotic patients treated with this sofosbuvir-based regimen is 100%.

The deterministic sensitivity analysis shows that overall the ICERs are sensitive to the discount rates for both costs and outcomes and the utility increment after achieving SVR. For some patient populations the results were also sensitive to changes in the SVR rate for cirrhotic patients. Nevertheless, the analyses consistently resulted in ICERs less than £20,000/QALY in

- GT1 TN IFN eligible: SOF + PEG-IFN-2a + RBV vs. boceprevir + PEG-IFN-2b + RBV

- GT2 TN/TE unsuitable for IFN: SOF + RBV vs. no treatment (NT)

- GT2 and 3 TE IFN eligible: SOF + RBV vs. NT.

The probability of sofosbuvir being cost-effective at a willingness to pay threshold of £20,000/QALY vary between indications:

- In GT1 IFN eligible patients it ranges from approximately 63-68% (against PEG-IFN-2a + RBV and telaprevir + PEG-IFN-2a + RBV respectively) to approximately 85% (against boceprevir + PEG-IFN-2b + RBV). For patients unsuitable to interferon the probability falls below 5%

- In GT2 patients it goes up to more than 90% across all indications and comparators except against PEG-IFN-2a + RBV where the probability is around 5% (TN IFN eligible) and 78% (TE IFN eligible)

- In GT3 patients it ranges from around 75% to 96% for patients who are TE IFN eligible and falls between 12% and 37% for those who are TN IFN eligible, TN unsuitable for IFN and TE unsuitable for IFN

- In GT4/5/6 patients the probability is approximately 24%.

Overall, sofosbuvir regimens, with and without IFN, were shown to be highly effective in preventing progression to advanced liver disease in patients with and without cirrhosis.

Table 1 Base case cost-effectiveness results – GT1

	GT1 TN IFN eligible				GT1 TN unsuitable for IFN	
	Sofosbuvir + PEG-IFN-2a+RBV (12 wks)	**PEG-IFN-2a+RBV (48 wks)**	**Telaprevir+PEG-IFN-2a+RBV**	**Boceprevir+PEG-IFN-2b+RBV**	**Sofosbuvir+RBV (24 wks)**	**No treatment**
Treatment costs (Drugs, AEs and monitoring; undiscounted)	£39,412	£12,046	£31,361	£30,134	£74,306	£821
Other costs	£4,711	£12,948	£7,473	£9,087	£9,822	£19,404
Total costs	£44,123	£24,994	£38,835	£39,221	£84,129	£20,225
Difference in total costs	N/A	£19,129	£5,288	£4,902	N/A	£63,903
LYG	20.2	19.3	19.9	19.8	19.5	18.7
LYG difference	N/A	0.9	0.3	0.4	N/A	0.8
QALYs	15.1	13.8	14.6	14.4	14.3	13.0
QALY difference	N/A	1.3	0.4	0.7	N/A	1.3
ICER	N/A	£14,930	£11,836	£7,292	N/A	£49,249

LYG, Life years gained; QALY(s), Quality-adjusted life year(s); ICER, Incremental cost-effectiveness ratio; wks: Weeks

Table 2 Base case cost-effectiveness results – GT2

	GT2 TN IFN eligible		GT2 TN unsuitable for IFN		GT2 TE IFN eligible			GT2 TE unsuitable for IFN	
	Sofosbuvir+RBV (12 wks)	**PEG-IFN-2a+RBV (24 wks)**	**Sofosbuvir+RBV (12 wks)**	**No treatment**	**Sofosbuvir+RBV (12 wks)**	**No treatment**	**PEG-IFN-2a+RBV (48 wks)**	**Sofosbuvir+RBV (12 wks)**	**No treatment**
Treatment costs (Drugs, AEs and monitoring; undiscounted)	£38,334	£7,039	£37,942	£817	£37,676	£159	£10,269	£37,580	£159
Other costs	£3,937	£7,453	£3,535	£20,609	£4,593	£20,612	£13,753	£3,888	£20,612
Total costs	£42,271	£14,492	£41,477	£21,426	£42,269	£20,771	£24,022	£41,468	£20,771
Difference in total costs	N/A	£27,779	N/A	£20,051	N/A	£21,498	£18,247	N/A	£20,697
LYG	21.6	21.1	20.4	18.6	20.2	18.6	19.3	20.3	18.6
LYG difference	N/A	0.5	N/A	1.8	N/A	1.6	0.9	N/A	1.7
QALYs	16.2	15.6	15.3	12.8	15.1	12.8	13.7	15.2	12.8
QALY difference	N/A	0.6	N/A	2.5	N/A	2.3	1.5	N/A	2.4
ICER	N/A	£46,324	N/A	£8,154	N/A	£9,274	£12,519	N/A	£8,591

LYG, Life years gained; QALY(s), Quality-adjusted life year(s); ICER, Incremental cost-effectiveness ratio; wks: Weeks

Table 3 Base case cost-effectiveness results – GT3

	GT3 TN IFN eligible		GT3 TN unsuitable for IFN		GT3 TE IFN eligible			GT3 TE unsuitable for IFN	
	Sofosbuvir+ PEG-IFN-2a+RBV (12 wks)	PEG-IFN-2a+RBV (24 wks)	Sofosbuvir+RBV (24 wks)	No treatment	Sofosbuvir+PEG-IFN-2a+RBV (12 wks)	No treatment	PEG-IFN-2a+RBV (48 wks)	Sofosbuvir+RBV (24 wks)	No treatment
Treatment costs (Drugs, AEs and monitoring; undiscounted)	£39,686	£6,836	£74,556	£843	£36,074	£173	£10,323	£73,792	£173
Other costs	£4,988	£12,868	£3,987	£22,563	£6,299	£22,566	£15,207	£7,776	£22,566
Total costs	£44,674	£19,704	£78,543	£23,406	£42,374	£22,740	£25,531	£81,568	£22,740
Difference in total costs	N/A	£24,970	N/A	£55,137	N/A	£19,634	£16,843	N/A	£58,828
LYG	21.5	20.3	20.3	18.3	20.1	18.3	19.1	19.8	18.3
LYG difference	N/A	1.2	N/A	2.1	N/A	1.9	1.0	N/A	1.5
QALYs	15.9	14.7	15.0	12.4	14.7	12.4	13.4	14.5	12.4
QALY difference	N/A	1.2	N/A	2.6	N/A	2.3	1.4	N/A	2.1
ICER	N/A	£20,613	N/A	£21,478	N/A	£8,557	£12,246	N/A	£28,569

LYG, Life years gained; QALY(s), Quality-adjusted life year(s); ICER, Incremental cost-effectiveness ratio; wks: Weeks

Table 4 Base case cost-effectiveness results – GT4/5/6

	GT 4/5/6 TN IFN eligible	
	Sofosbuvir+PEG-IFN-2a+RBV (12 wks)	**PEG-IFN-2a+RBV (48 wks)**
Treatment costs (Drugs, AEs and monitoring; undiscounted)	£39,941	£10,797
Other costs	£6,631	£11,834
Total costs	£46,573	£22,631
Difference in total costs	N/A	£23,942
LYG	19.8	19.5
LYG difference	N/A	0.3
QALYs	14.8	13.9
QALY difference	N/A	0.9
ICER	N/A	£26,797

LYG, Life years gained; QALY(s), Quality-adjusted life year(s); ICER, Incremental cost-effectiveness ratio; wks: Weeks

Table 5 Incremental cost-effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. baseline	Incremental analysis
GT1 TN IFN eligible						
PEG-IFN-2a+RBV (48 wks)	£24,994	13.8	£0	0.0	NA	NA
Telaprevir+PEG-IFN-2a+RBV	£38,835	14.6	£13,841	0.8	£16,587	Weakly dominated
Boceprevir+PEG-IFN-2b+RBV	£39,221	14.4	£14,227	0.6	£23,360	Dominated
Sofosbuvir + PEG-IFN-2a + RBV (12 wks)	£44,123	15.1	£19,129	1.3	£14,930	£14,930
GT1 TN unsuitable for IFN						
No treatment	£20,225	13.0	£0	0.0	NA	NA
Sofosbuvir+RBV (24 wks)	£84,129	14.3	£63,903	1.3	£49,249	£49,249
GT2 TN IFN eligible						
PEG-IFN-2a+RBV (24 wks)	£14,492	15.6	£0	0.0	NA	NA
Sofosbuvir+RBV (12 wks)	£42,271	16.2	£27,779	0.6	£46,324	£46,324
GT2 TN unsuitable for IFN						
No treatment	£21,426	12.8	£0	0.0	NA	NA
Sofosbuvir+RBV (12 wks)	£41,477	15.3	£20,051	2.5	£8,154	£8,154
GT2 TE IFN eligible						
No treatment	£20,771	12.8	£0	0.0	NA	NA
PEG-IFN-2a+RBV (48 wks)	£24,022	13.7	£3,251	0.9	£3,778	£3,778
Sofosbuvir+RBV (12 wks)	£42,269	15.1	£21,498	2.3	£9,274	£12,519
GT2 TE unsuitable for IFN						
No treatment	£20,771	12.8	£0	0.0	NA	NA
Sofosbuvir+RBV (12 wks)	£41,468	15.2	£20,697	2.4	£8,591	£8,591
GT3 TN IFN eligible						
PEG-IFN-2a+RBV (24 wks)	£19,704	14.7	£0	0.0	NA	NA

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. baseline	Incremental analysis
Sofosbuvir+PEG-IFN-2a+RBV (12 wks)	£44,674	15.9	£24,970	1.2	£20,613	£20,613
GT3 TN unsuitable for IFN						
No treatment	£23,406	12.4	£0	0.0	NA	NA
Sofosbuvir+RBV (24 wks)	£78,543	15.0	£55,137	2.6	£21,478	£21,478
GT3 TE IFN eligible						
No treatment	£22,740	12.4	£0	0.0	NA	NA
PEG-IFN-2a+RBV (48 wks)	£25,531	13.4	£2,791	0.9	£3,037	£3,037
Sofosbuvir+PEG-IFN-2a+RBV (12 wks)	£42,374	14.7	£19,634	2.3	£8,557	£12,246
GT3 TE unsuitable for IFN						
No treatment	£22,740	12.4	£0	0.0	NA	NA
Sofosbuvir+RBV (24 wks)	£81,568	14.5	£58,828	2.1	£28,569	£28,569
GT4/5/6 TN IFN eligible						
PEG-IFN-2a+RBV (48 wks)	£22,631	13.9	£0	0.0	NA	NA
Sofosbuvir+PEG-IFN-2a+RBV (12 wks)	£46,573	14.8	£23,942	0.9	£26,797	£26,797

QALY, Quality-adjusted life year; ICERs, Incremental cost-effectiveness ratios; wks: Weeks

Conclusion

Sofosbuvir is the first nucleotide polymerase inhibitor with a pan genotypic activity and high barrier to resistance which offers greater than 90% cure rates in treatment-naïve patients based upon 12 weeks of treatment across all genotypes.

Sofosbuvir also enables the first all oral treatment option based on 24 weeks of treatment for those unsuitable to interferon who previously had limited or no treatment options.

In addition, to date there are no adverse drug reactions specific to sofosbuvir.

The pan genotypic activity and high barrier to resistance of sofosbuvir along with its tolerability should ensure that sofosbuvir is an important backbone component of future therapeutic regimens for chronic HCV infection, both in combination with PEG - IFN + RBV or as the first available all-oral therapy option.

Sofosbuvir-based regimens offer a favourable cost-effectiveness profile compared with current standards of care. Across all HCV genotypes (GT1–6), including patients with compensated cirrhosis, and irrespective of treatment experience or IFN eligibility, sofosbuvir is associated with overall QoL gains (QALYs), a greater probability of cure (SVR rates), and reduction in death rate.

Compared with current standards of care sofosbuvir offers a significant step change in treatment of patients with HCV making successful HCV cure a realistic probability for a higher proportion of patients. Sofosbuvir as a short-course, well-tolerated and effective therapy option extends treatment to reach HCV-infected patients who would not have been eligible for, or able to tolerate, current IFN-based regimens. Through improving cure rates together with increasing the number of patients eligible for treatment sofosbuvir has 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.

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.

Generic name: Sofosbuvir

Approved name: Sovaldi

Therapeutic class: Uridine nucleotide analogue NS5B polymerase inhibitor

A copy of the draft SmPC is provided in Appendix 1.

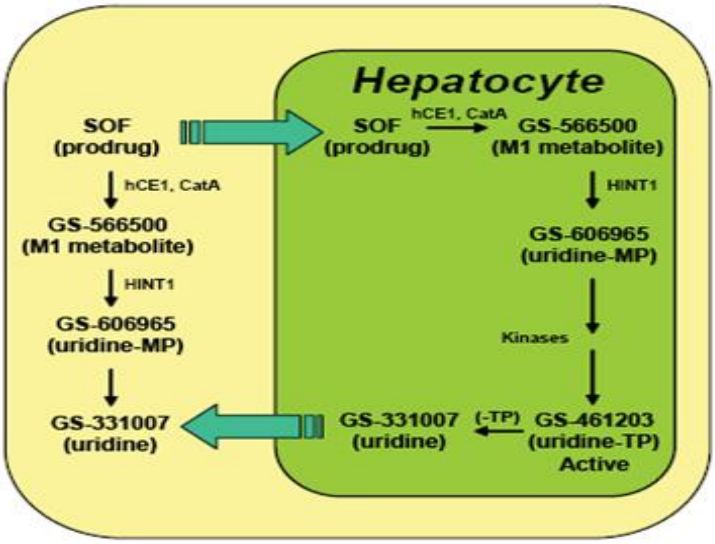
1.2 What is the principal mechanism of action of the technology?

Sofosbuvir is a first-in-class oral uridine nucleotide. It is a pan-genotypic inhibitor of the hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase which is essential for viral replication.

Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism within the hepatocytes to form a pharmacologically active uridine triphosphate which can be incorporated into the HCV RNA by the NS5B RNA-dependent RNA polymerase and cause chain termination during replication of the viral genome.

Details of the metabolism of sofosbuvir are provided in Figure 1.

Figure 1: Sofosbuvir metabolism



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).***

Regulatory submission to EMA: April 2103

Committee for Medicinal Products for Human Use (CHMP) positive opinion: 6th November 2013

Marketing authorisation: 17th January 2014

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).

The European Public Assessment Report (EPAR) is anticipated and will be provided once available.

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

Sofosbuvir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

NOTE: Within EU regulatory Assessment Report it was recognised by regulators that '*Unlike several other DAAs, SOF has pangenotypic activity and a high barrier to resistance. On treatment viral breakthrough is very uncommon with SOF combination therapy. Furthermore, no selection of clinically relevant resistance to SOF has hitherto been shown. This quality of SOF makes it a potential backbone for a number of different combination regimens. Available data, though scarce, are indicative that retreatment with SOF-based therapy (in combination with more drugs, or for a longer duration), may be effective in patients that fail a first course'*.

On this basis it was recommended that the therapeutic indication for SOF should be in combination with other medicinal products without specification of the specific combination products.

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.

Details of the ongoing studies relevant to the anticipated licence indication due to completed within the next 12 months are provided below.

Study number	Details	Estimated date final results will be available
P7977-0523 (Parts 4 and 5) (ELECTRON)	A Multi-center, Open-Labeled Exploratory Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of sofosbuvir 400 mg and Ribavirin for 12 Weeks With and Without Pegylated Interferon in Treatment Naïve Patients with Chronic HCV Infection Genotype 2 or Genotype 3	Q2 2014
P7977-1910	Part A: Drug Interaction Study between sofosbuvir and Antiretroviral Therapy (ARV) Combinations of Efavirenz, Tenofovir and Emtricitabine; Efavirenz, Zidovudine and Lamivudine; Atazanavir/ritonavir, Tenofovir and Emtricitabine; Darunavir/ritonavir, Tenofovir and Emtricitabine; Raltegravir, Tenofovir and Emtricitabine in Human Immunodeficiency Virus and Hepatitis C Virus (HIV/HCV) Co-infected Patients. Part B: A Phase 2, Open-Label Study to Investigate the Efficacy and Safety of sofosbuvir with Peginterferon Alfa 2a and Ribavirin for 12 Weeks in Treatment-Naïve Subjects in Human Immunodeficiency Virus and Hepatitis C Virus (HIV/HCV) Co-infected Patients	Q2 2014
P7977-2025	An Open-Label Study to Explore the Clinical Efficacy of sofosbuvir with Ribavirin Administered Pre-Transplant in Preventing Hepatitis C Virus (HCV) Recurrence Post-Transplant	Q1 2015
GS-US-334-0114	A Phase 2, Randomised, Open-Label Study to Evaluate the Safety and Efficacy of Sofosbuvir Plus Ribavirin Administered for Either 12 or 24 Weeks in Treatment-Naïve and Treatment-Experienced Egyptian Adults with Chronic Genotype 4 HCV Infection	Q3 2014
GS-US-334-0118	A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir plus Ribavirin in Treatment-Naïve and Treatment-Experienced Japanese Subjects with Chronic Genotype 2 HCV Infection	Q4 2014
GS-US-334-0123 (PHOTON-1)	A Phase 3, Open-label Study to Investigate the Efficacy and Safety of sofosbuvir plus Ribavirin for 12 Weeks in Treatment-Naive or Interferon (IFN) Intolerant Subjects with Chronic Hepatitis C Virus (HCV) and Human Immunodefiency Virus (HIV) Co Infected Subjects.	Q3 2014
GS-US-334-0124 (PHOTON-2)	A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir plus Ribavirin in Chronic Genotype 1, 2, 3 and 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co infected Subjects	Q1 2015
GS-US-334-0126	A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of sofosbuvir and Ribavirin for 24 weeks in Subjects with Recurrent Chronic HCV Post Liver Transplant	Q1 2015
GS-US-334-0133 (VALENCE)	A Phase 3, Multicenter, Randomised, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of sofosbuvir + Ribavirin for 12 Weeks in Treatment Naïve and Treatment Experienced Subjects with Chronic Genotype 2 or 3 HCV Infection	Q3 2014
GS-US-334-0138	A Phase 3, Randomised, Open-Label, Study to	Q1 2015

	Evaluate the Safety and Efficacy of Sofosbuvir Plus Ribavirin Administered for Either 12 or 24 Weeks in Treatment-Naïve and Treatment-Experienced Egyptian Adults with Chronic Genotype 4 HCV Infection	
GS-US-334-0151 (LONESTAR 2)	A Phase 2, Open-Label study of Sofosbuvir in Combination with PEG and Ribavirin for 12 Weeks in Treatment Experienced Subjects with Chronic HCV Infection Genotype 2 or 3	Q1 2014

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

Date of UK availability: 17th January 2014 - in line with Marketing Authorisation

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

Yes:

- Approval across the European Union granted 16th January 2014
- Food and Drugs Administration (FDA) approval granted 6th December 2013
- Canadian approval from Health Canada granted 13th December 2013

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?

A submission was made to the Scottish Medicines Consortium (SMC) on 6th January 2014. Advice is expected to be published on the SMC website Q2 2014.

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 6 Unit costs of technology being appraised

Pharmaceutical formulation*	Film-coated tablet
Acquisition cost (excluding VAT)	For a 28 day pack the acquisition cost is £11,660.98
Method of administration	Oral
Doses	400 mg
Dosing frequency	Once a day with food
Average length of a course of treatment	12 or 24 weeks according to genotype and status with regards to interferon. For patients with GT1, 3 to 6 the standard regimen is sofosbuvir + ribavirin† + peginterferon alpha for 12 weeks or in patients unsuitable for interferon** sofosbuvir+ribavirin for 24 weeks. For patients with GT2 the standard regimen is sofosbuvir + ribavirin12 weeks
Patients with (genotype) GT 1,4,5 or 6 CHC	Sofosbuvir + ribavirin† + peginterferon alpha 12 weeks[a,b]
	Sofosbuvir + ribavirin† 24 weeks (only for use in patients ineligible or intolerant to peginterferon alpha)
Patients with GT 2 CHC	Sofosbuvir + ribavirin† 12 weeks[b]
Patients with GT 3 CHC	Sofosbuvir + ribavirin† + peginterferon alpha 12 weeks[b]
	Sofosbuvir + ribavirin† 24 weeks
Patients with CHC awaiting liver transplantation	Until liver transplantation. Duration should be guided by an assessment of the potential benefits and risks for the individual patient
Cost of a course of treatment (sofosbuvir only)	12 week course = £34,982.94 24 week course = £69,965, 88
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	Dose reduction is not recommended

*Includes patients co-infected with human immunodeficiency virus (HIV)

**Approximately 14% of patients

For previously treated patients with HCV GT1, no data exists with the combination of sofosbuvir, ribavirin and peginterferon alpha

Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies e.g. advanced fibrosis/ cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peginterferon alpha and ribavirin therapy.

† The dose of ribavirin when used in combination with sofosbuvir is weight-based (< 75 kg= 1,000 mg and ≥ 75 kg = 1,200 mg) and administered orally in two divided doses with food.

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. No additional tests or investigations are needed for the selection of patients or administration of sofosbuvir.

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

Less monitoring is required with sofosbuvir-based regimens compared with current standard of care:

There is no requirement for response-guided therapy

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 (Incivo SmPC, Pegasys SmPC, Victrelis SmPC, Viraferon SmPC)[20-23]

By comparison the high proportion of patients achieving both a rapid virologic response (after 4 weeks of treatment) and an end of treatment response means that on-treatment monitoring of HCV RNA and response-guided therapy are not required for sofosbuvir-based regimens. This should simplify patient management considerably relative to standards of care and also reduce the need for frequent on-treatment viral load monitoring and clinic visits.

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?

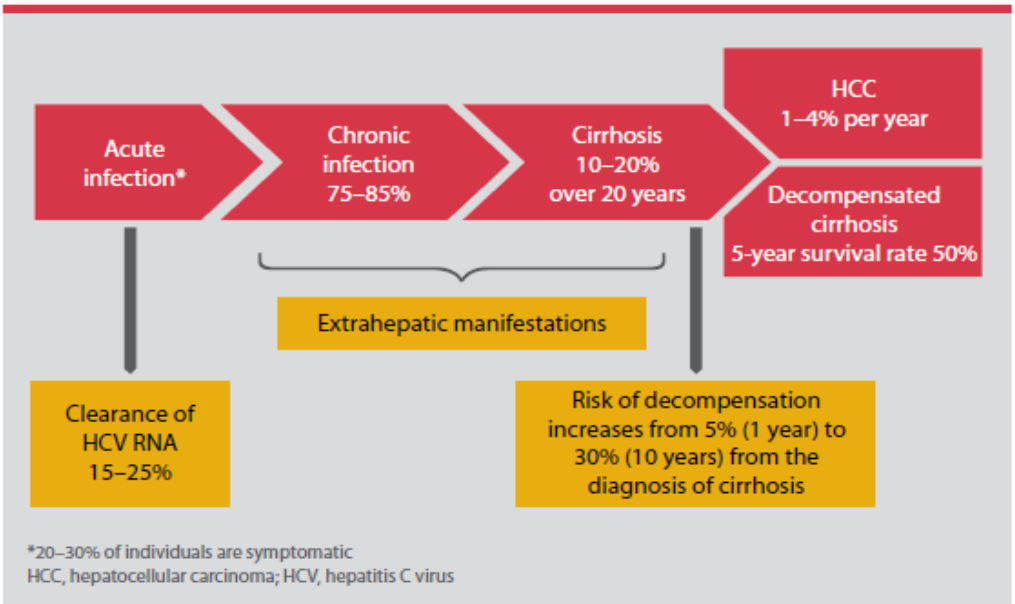
Sofosbuvir will be used in combination with peginterferon alfa (2a or 2b) and /or ribavirin (RBV) as detailed in Table 6 above. Within the clinical trial programme peginterferon alfa 2-a (PEG-IFN-2a) was used.

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.

Hepatitis C is associated with significant morbidity, mortality and economic burden. It is a progressive disease caused by the hepatitis C virus (HCV) which infects the liver. Acute infection is generally asymptomatic and between 15-25% of acutely affected individuals will gradually show a decrease in virus levels (Chen and Morgan 2006)[1]. The remaining 75-85 % go on to develop chronic HCV (CHC) defined as persistent, detectable serum HCV RNA for a period greater than 6 months (Figure 2). Between 5% and 25% of individuals with CHC 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 2). Compared with non-infected patients, the risk of developing HCC is 17-fold higher in HCV infected patients with patients diagnosed with HCC having a 33% probability of death during the first year (EASL 2014, de Oliveria *et al.* 2009)[13;24]. CHC is the most common cause of cirrhosis and the most common indication for liver transplantation in Europe (Zaltron *et al*. 2012)[4].

Figure 2: Hepatitis C disease progression (Chen and Morgan 2006)[1]



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, sex, the presence of co-morbidities such as obesity or insulin resistance, and co-infection with hepatitis B virus (HBV) or HIV (Zaltron *et al*. 2012)[4]. 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 CHC until they present with the complications of end-stage liver disease or HCC. 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 extrahepatic manifestations, including autoimmune disease, skin reactions, renal injury and neuropathy; it is estimated that up to 76% of patients with CHC experience at least one such manifestation (Chen and Morgan

2006, Himoto and Masaki 2012)[1;2]. These extrahepatic manifestations contribute considerably to the overall disease burden in CHC patients (Lee *et al.* 2012)[3].

CHC also leads to impairment in quality of life (QoL) with patients feeling unwell in terms of both their physical and mental health (Foster *et al.* 1998, Akobeng and Davison 2000)[5;6]. In addition to a reduced quality of life patients also have to manage with the social stigma associated with CHC (Zachs *et al*. 2006)[7].

There are 6 major genotypes (GT 1, 2, 3, 4, 5 and 6.) and several subtypes (labelled a, b, c, etc.). GT1 is the most prevalent in the UK accounting for 40-50% of cases. GTs 2 and 3 (GT2/3) account for 40%- 50% of cases and GT4, 5 and 6 for the remaining infections of 5% (Public Health England 2013, NICE TA75)[8;25]. In England, sentinel surveillance data from 2008 to 2012 show GT1 (46%) and GT3 (43%) predominating with other genotypes comprising of just over 10% of infections (Public Health England 2013)[8]. Response to treatment, rate of disease progression and the choice of therapy for HCV infection is strongly influenced by HCV genotype.

CHC is associated with a considerable health burden with an estimated 215,000 individuals chronically infected with hepatitis C in the UK (Public Health England 2013)[8] including 160,000 people in England (Public Health England 2013)[8]. While levels of HCV infection are declining the prevalence of hepatitis C 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 (Public Health England 2013)[8]. 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 (Public Health England 2013)[8].

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 (Poynard *et al.* 2003)[9]. 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 (NICE TA200)[26]. 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 (Ng and Saab 2011, van der Meer *et al*. 2012, van der Meer *et al*. 2013)[10-12].

Currently two main treatment options provide the standard of care for patients with CHC:

- Protease inhibitors telaprevir and boceprevir in combination with peginterferon and ribavirin for patients with GT1

- Peginterferon plus ribavirin (PEG-IFN + RBV). Monotherapy PEG-IFN is recommended for patients who are unable to tolerate ribavirin or for whom ribavirin is contraindicated

While these current treatment options are successful and provide a cure for some patients they are not successful in a substantial proportion (EASL, 2014)[13]. 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 (Shah *et al*. 2013)[14]. In addition for those patients who are inteferon-unsuitable (including those in whom interferon is contraindicated, who are interferon intolerant or who are unwilling to take interferon) there is no treatment currently available. There is a need for new therapies which address these issues. With the increasing burden of CHC the effective treatment of patients is essential in order to avoid progression of the disease and the associated complications, including excess mortality

Further details on the current treatments, associated NICE guidance and current unmet need are provided in Sections 2.4 and 2.5.

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 estimated number of patients in England and Wales who will be eligible for treatment with sofosbuvir is XXXX. This figure is based on the following:

- Currently only 3% of chronically infected patients are treated (Public Health England 2013)[8]. In England an estimated 27,500 patients were treated between 2006 and 2011 with peginterferon as part of NICE recommended combination therapy.

- Due to its pan-genotypic activity, improved efficacy and safety profile compared with current treatments sofosbuvir could result in an estimated XXXXXXXX to XXXXX patients being successfully treated.

Further details on patient numbers will be provided in Section 8.1 of the full submission document. The opportunity to treat more patients is anticipated to have a significant 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 (Public Health England 2013)[8].

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 CHC is associated with increased morbidity and mortality, published data on the actual life expectancy of people with CHC is limited and dependent on the degree of liver fibrosis and ongoing addictive behaviour especially alcohol.

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 (Neal 2007)[27].

For patients with liver disease data from the British Society of Gastroenterology highlight that average age of someone dying with liver disease is 59 years compared to 82-84 years for heart and lung disease and stroke (BSG, 2013)[28].

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[29]	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[30]	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[26]	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 2006[31]	Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. This is an extension of the guidance given in NICE technology appraisal guidance 75	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. 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 2004[25]	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.

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 increase risk of infection'* (PH43, March 2013)[32]. 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.

A NICE clinical guideline (Hepatitis C: Diagnosis and management of hepatitis C) is in development. The current clinical pathway of care takes into account the European Association for the Study of the Liver (EASL) guidelines (EASL 2014)[13] and NICE Technology Appraisals (TA75, 106, 200, 252 and 253)[25;26;29-31]

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

NICE guidance on hepatitis C (TA75, TA106)[25;31] recommends that standard treatment for the majority of people with CHC, regardless of disease severity, is combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b. Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended for patients who are unable to tolerate ribavirin or for whom ribavirin is contraindicated.

NICE guidance on hepatitis C (TA200)[26] also recommends that people who have been previously treated with peginterferon alfa and ribavirin or with peginterferon alfa monotherapy have an option to receive further courses of peginterferon alfa and ribavirin. Shortened courses of combination therapy are also recommended as an option for certain patient subgroups.

For people with genotype 1 CHC, who have not been previously treated or who have been previously treated, NICE guidance recommends telaprevir in combination with peginterferon alfa and ribavirin (TA252)[30] or boceprevir in combination with peginterferon alfa and ribavirin (TA253)[29].

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.

<u>Sofosbuvir</u>

Sofosbuvir represents a new breakthrough treatment for patients with CHC offering:

- A treatment option which is effective across all genotypes and which does not require response guided therapy
- A treatment that allows more patients the opportunity of a cure:

- ≥90% of treatment naïve GT 1, 3, 4,and 6 adults cured within 12 weeks of sofosbuvir + peginterferon + ribavirin (12 weeks with an all oral sosfosbuvir + ribavirin regime for GT2)

- 97% of treatment naïve GT2 adults cured with 12 weeks of sosfosbuvir + ribavirin

- A simple and shorter treatment duration compared with current standard of care

- First all oral 24 week option across all genotypes for those patients unsuitable for interferon

- A side effect profile similar to placebo and superior to the current standard of care

- Minimal risk of viral resistance. No viral resistance was seen in any of the patients treated with sofosbuvir in combination with peginferon or ribavirin in the pivotal Phase 3 studies

- Sofosbuvir has a unique mechanism of action which allows it to be administered in all patients with CHC across all HCV genotypes with minimal risk for the emergence of viral resistance

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

While CHC is a curable disease there remains a significant unmet need with regards to treatment and while current treatment options are successful and provide a cure for some patients they are not successful in a substantial proportion of patients (EASL 2014)[13]. Limitations associated with the current treatments are provided 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. Of all diagnosed HCV patients, only 20% (approximately) actually commence treatment and only 3% to 4% of the total diagnosed population achieves a SVR (North *et al.* 2013)[16]. For those treated patients who do not achieve a SVR, retreatment with the same regimen is not recommended, leaving such patients without 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 peginterferon or ribavirin (EASL 2014)[13].

The current standard of care treatments is 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 (all genotypes) remain untreated due to contraindications to interferon therapy such as hepatic decompensation, autoimmune disease and psychiatric illness (Falck-Yteer Y *et al.* 2002)[15].

Protease-based triple therapy

In patients infected with HCV GT1, while the relatively new treatment regimen of telaprevir or boceprevir in combination with peginterferon and ribavirin improves cure rates and in some patients shortens treatment duration, it is associated with a number of disadvantages. These include an increase in 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 (NICE TA 252 and 253 2012, Wyles 2012)[29;30;33].

Triple therapy with both telaprevir and boceprevir is associated with an increase in adverse events over and above those seen with peginterferon in combination with ribavirin alone (see Table 7).

Table 7: Side effect profiles of telaprevir and boceprevir

Direct-acting antiviral agent	Side-effect profile
Telaprevir	Rash,* anaemia,* nausea,* haemorrhoids,* diarrhoea,* anorectal discomfort,* pruritus,* dysgeusia,* fatigue,* vomiting,* DRESS, Steven–Johnson syndrome
Boceprevir	Fatigue, anaemia, nausea, headache, dysgeusia, dry mouth, vomiting, diarrhoea

*Most common side effects; DRESS, drug rash with eosinophilia and systemic symptoms

In addition to the common side effects of telaprevir, 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 (Shah *et al.* 2013)[14]. 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, the 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 high pill burden with both telaprevir (two or three

375 mg tablets, twice or three times daily) and boceprevir (four 200 mg capsules, three times daily), and the need to take each medication with food (Incivo SmPC, Victrelis SmPC)[20;22] which may adversely affect adherence to therapy (Kiser *et al* 2012). The complexity of treatment regimens with telaprevir and boceprevir (e.g. the need for lead-in treatment or extended treatment with peginterferon + ribavirin depending on response) and the need for response guided therapy also complicate treatment (Incivo SmPC, Victrelis SmPC)[20;22]. Overall, the total length of treatment with telaprevir 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 (Incivo SmPC, Victrelis SmPC)[20;22].

Both telaprevir and boceprevir are substrates and inhibitors of the hepatic enzyme cytochrome P450 3A and the drug transporter, P-glycoprotein, which predisposes

them to a wide range of drug-drug interactions (Kiser *et al*. 2012)[34] Interactions with drugs such as immunosuppressants and antiretrovirals 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 (Kiser *et al*. 2012)[34].

A further and important consideration with boceprevir and telaprevir is their low barrier to resistance. Initial studies of telaprevir and boceprevir showed rapid emergence of resistant mutants and complete replacement of wild-type virus with drug resistant variants in patients with breakthrough viraemia (Wyles 2012)[33]. Overall, in Phase 3 telaprevir and boceprevir triple therapy trials in treatment-naive patients, resistant variants were detected in 50-75% of patients not achieving an SVR, and in 90% of those with virological failure (Wyles 2012)[33]. Moreover, such variants arising in response to either agent confer cross resistance to the other drugs from the same class (Wyles 2012)[33].

Peginterferon plus ribavirin

The primary limitation of peginterferon plus ribavirin treatment is its association with severe and often intolerable side effects. These include influenza-like symptoms, fatigue, depression, skin reactions and haematological events (anaemia, thrombocytopenia and neutropenia) (EASL 2014)[13].

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 (EASL 2014)[13]. In clinical practice evidence suggests that only around 19% of patients are considered treatment eligible for peginterferon therapy and received treatment (North *et al.* 2013)[16]. 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 (North *et al.* 2013)[16].

Unmet need

There is a clear medical need for new treatments which provide a shorter, simpler, better tolerated and more effective pan genotypic regimens with a high likelihood of success, which have a high barrier to resistance and no drug to drug interactions and which can be used for the treatment of naïve and treatment experienced patients with CHC including those unsuitable for interferon.

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

The main comparators are as follows:

- Protease inhibitors

  Telaprevir or boceprevir, in combination with peginterferon alfa plus ribavirin are recommended by NICE and are appropriate comparators for patients with GT1.

- peginterferon and/or ribavirin

- No available treatment

For a significant proportion of patients there are no alternative treatment options (i.e. those unsuitable for interferon – such as those who are medically ineligible, those who are interferon-intolerant or unwilling to take interferon). For such patients the alternative is a 'no treatment' or placebo comparator.

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

There are no adverse events specific to sofosbuvir. In clinical trials sofosbuvir demonstrated a side effect profile similar to placebo and superior to the current standard of care. The adverse events and laboratory safety profile of sofosbuvir in combination with ribavirin and peginterferon + ribavirin are similar to that expected with ribavirin and peginterferon + ribavirin alone. Rates of treatment discontinuation and dose reduction with sofosbuvir containing regimens in the phase III trials were lower than those usually observed with the peginterferon and ribavirin.

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.

Sofosbuvir will be used in combination with the current standard of care (peginterferon +/- ribavirin) in an already established hepatitis C treatment pathway where the required clinical infrastructure is in place. No costs are associated with administration and as response guided therapy is not required it is anticipated that monitoring costs will be reduced.

The shorter dosing schedules for sofosbuvir-based regimens and improved tolerability profile compared with current standard of care treatment 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 the fact that response guided therapy is not required with sofosbuvir-based regimens 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**

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

Not applicable.

3.1.2 How has the analysis addressed these issues?

Not applicable.

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.

Sofosbuvir offers a step-change in the efficacy, safety and tolerability for the treatment of patients with HCV making successful HCV cure a realistic probability for a high proportion of patients including those who currently have no treatment options.

Sofosbuvir meets the five criteria for step-change innovation as laid out in the Kennedy Report 2009 (Kennedy 2009)[35], such that sofosbuvir:

- Significantly and substantially improves the way that a current need is met. *Sofosbuvir demonstrates:*
    - *efficacy across all genotypes*
    - *a placebo-like side effect profile*

  and also provides a new treatment option across all genotypes for those patients unsuitable for interferon.
- Meets a need which the NHS has identified as being important. *The recent NHS Outcomes Framework reflects the government commitment to reducing mortality due to liver disease in the under-75s. By proving a cure treatment with sofosbuvir has the potential to reduce HCV related liver disease and associated mortality.*

- Has a robust evidence base providing research on the populations in which the product is effective. *The sofosbuvir clinical programme* includes *trials across all genotypes and incorporates relevant subgroups*.
- Has demonstrated an appropriate level of effectiveness. *Sofosbuvir provides a treatment option for wider patient pool than the current standard of care.*

Sofosbuvir represents a breakthrough treatment for HCV providing patients and clinicians with:

- The first pan-genotypic treatment which offers predictable rates of sustained virological response across all genotypes and which does not require response guided therapy
- A simple once a day tablet with few dosing restrictions
- A treatment which allows more patients the opportunity of a cure:
    - ≥90% of treatment naïve GT1, 4 and 6 adults cured within 12 weeks of sofosbuvir + peginterferon + ribavirin (12 weeks with an all oral SOF+RBV regimen for GT2)
    - 97% of treatment naïve GT2 adults cured with 12 weeks of sofosbuvir + ribavirin
- A shorter treatment duration compared with current standard of care
- First all oral 24 week option across all genotypes for those patients unsuitable for inteferon
- A side effect profile similar to placebo and superior to the current standard of care
- Minimal risk of viral resistance. No viral resistance was seen in any of the patients treated with sofosbuvir in combination with PEG-IFN or RBV in the pivotal Phase 3 studies
- Sofosbuvir has a unique mechanism of action which allows it to be administered in all patients with chronic HCV across all HCV genotypes with minimal risk for the emergence of viral resistance. This means that sofosbuvir can be re-used (in combination with other products) if required
- A lack of significant drug interactions with immunosuppressant drugs and commonly used antiretrovirals meaning that sofosbuvir can be used safely in liver transplant patients and patients co-infected with HIV.

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.

Health related benefits that are not included in the QALY calculation include the reduction in onward transmission of the HCV through rapid clearance of the virus from the body due to effective treatment, together with the potential for reversal of liver fibrosis once cured of HCV.

Improving cure rates together with increasing the number of patients eligible for treatment sofosbuvir has the potential to positively impact on public health via a positive impact on the overall prevalence of HCV and reducing long-term burden to the NHS of HCV. It should be noted that the EMA accepted an accelerated

regulatory approval process for sofosbuvir, a designation only granted to those medicines of major public health interest.

Additional benefits associated with sofosbuvir within the economics model submitted but which are not taken into account in the QALY calculation include the benefits of sofosbuvir in reducing the risk of HCC and mortality.

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.

Onward transmission

Data to support this are the rapid reductions in HCV RNA to <LLOQ (lower limit of quantitation) regardless of GT and which are sustained post-treatment in the majority of patients (see Section 6) together with public health information re: rates of transmission from individuals infected with HCV.

Reversal of liver fibrosis and reduction in risk of HCC

Published evidence supports the fact that a 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 (Ng and Saab 2011, van der Meer et al. 2012, van der Meer et al. 2013)[10-12].

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with chronic hepatitis C	As per the scope
Intervention	• Sofosbuvir in combination with peginterferon alfa and ribavirin • Sofosbuvir in combination with ribavirin	As per the scope
Comparator(s)	• Peginterferon alfa with ribavirin • Telaprevir in combination with peginterferon (for genotype 1 only) • Boceprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only) • Best supportive care (including treatments for manage the liver disease with a treatment for the hepatitis C)	As per the scope.
Outcomes	• Sustained virological response • Mortality • Adverse effects of treatment • Health-related quality of life	As per 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
Subgroups to be considered	If evidence allows the following subgroups will be considered: • Co-infection with HIV • Response to previous treatment (non-response, partial response, relapsed)	Evidence for both subgroups will be presented.
Special considerations, including issues related to equity or equality	None stated	As per the scope

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.

A full systematic review has been carried out to identify all randomised controlled trials comparing sofosbuvir with peginterferon and/or ribavirin in patients with CHC. Full details of the search strategies are provided in Appendix 2, Section 10.2.

Databases searched included:

- PubMed
- Excerpta Medica Database (EMBASE®)
- Cochrane

The following conference proceedings were specifically searched from 2013 onwards:

- American Association for the Study of Liver Disease (AASLD)
- European Association for the Study of the Liver (EASL)

To be included in the review trials had to meet pre-defined eligibility criteria; studies were to have a full text English publication/poster to be included; full inclusion criteria are listed below in Table 8.

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. Each citation was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded at this 'first pass,' and where unclear, citations were included. 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 two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Data presented in the studies included at this stage were extracted in parallel by two independent reviewers, with reconciliation of any differences by a third independent reviewer. Where 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 of patients.

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 8: Eligibility criteria used in search strategy

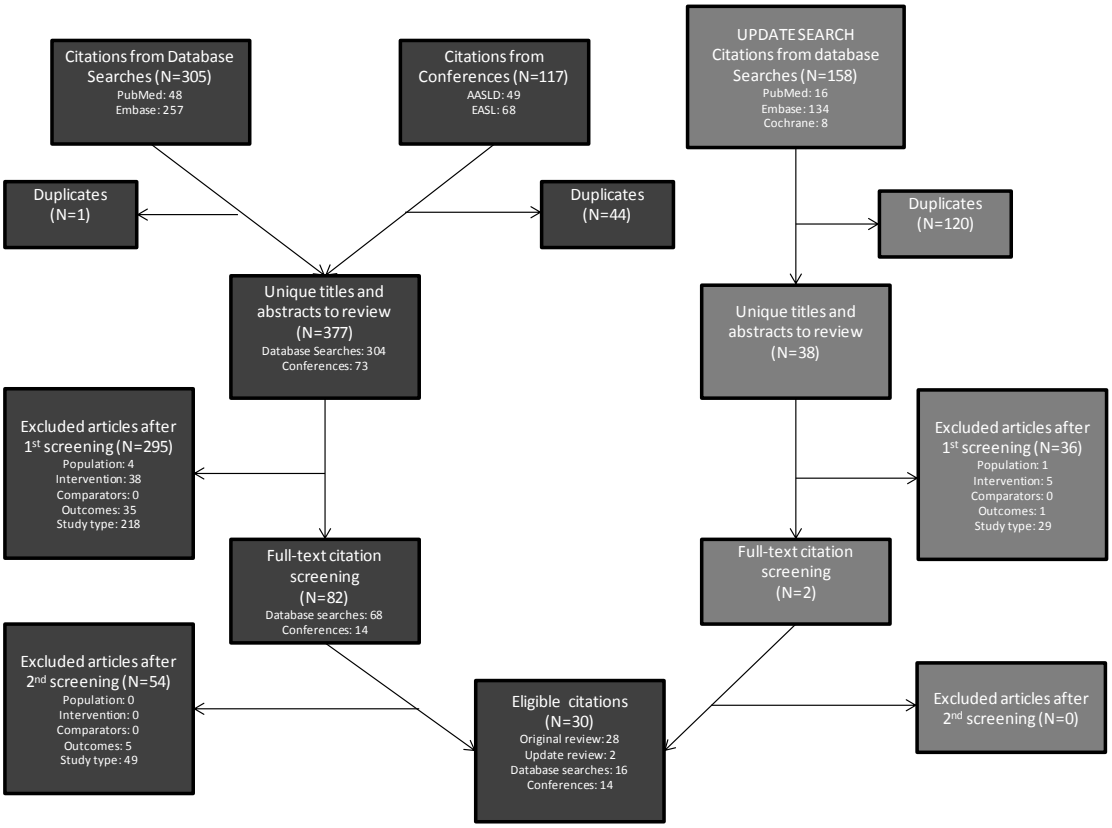
Inclusion criterion	Inclusion criteria	Details	Comments
1	Patient population	Chronic hepatitis C patients	In line with the draft scope
2	Intervention	Sofosbuvir	
3	Comparison therapy	Any comparison therapy	Single-arm studies were included
4	Patient relevant outcomes	SVR12, SVR24	Sustained virologic response (SVR): absolute number or percentage for SVR 12 and/or 24 weeks after end of treatment
5	Study types	All phase 2 or 3 clinical trials - phase 2 or 3 randomised controlled trials - observational studies	Randomised controlled trial (RCT) - Does not have to be blinded (open-label and single-blinded studies are accepted)
6	Publication type	full-text journal publications that are available only abstracts that report SVR12 or SVR24	
7	Language	No language limits	
Exclusion criterion	**Exclusion criteria**	**Details**	**Comments**
1	Patient population	Not patients with chronic hepatitis C in relevant genotypes	
2	Intervention	Not a trial assessing the efficacy of sofosbuvir	
3	Comparison therapy	No limit	
4	Patient relevant outcomes	Does not report SVR	
5	Study types	Not clinical trial (phase 2/3 RCT or observational study)	Excluded meta-analyses, pooled analyses and systematic reviews - were flagged for cross-checking references and no additional references were identified. Excluded the following studies: • Pharmacokinetic studies • Pilot studies • Animal studies • In vitro studies • Case studies • Pharmacoeconomic studies

6	Publication type	Not publication of RCT (e.g., review, letter, commentary)	Excluded conference abstracts which did not report SVR12 or SVR24

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.

Search of the literature database identified 30 eligible citations covering 20 clinical studies and one compassionate use programme (see Sections 6.2.3 and 6.2.4).

Figure 3: Consort flow diagram of the systematic review



An additional literature search focusing on current treatments was performed as part of a mixed treatment comparison (see Appendix 4.0). This did not highlight any additional sofosbuvir trials.

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.

Trial Number Acronymn	Primary data source	Additional reference source(s)
Phase III		
GS-US-334-0110 NEUTRINO	Lawitz *et al*. 2013a[17]	Lawitz *et al*. 2013b[36] Patel *et al* 2013[37] Yoshida *et al*. 2013[38]
P7977-1231 FISSION	Lawitz *et al*. 2013a[18]	Patel *et al* 2013[37] Yoshida *et al*. 2013[38]
GS-US-334-0108 FUSION	Jacobson *et al.* 2013a[18]	Patel *et al* 2013[37] Yoshida *et al*. 2013[38]
GS-US-334-0107 POSITRON	Jacobson *et al.* 2013a[18]	Jacobson *et al.* 2013b [39] Patel *et al* 2013[37] Yoshida *et al*. 2013[38]
GS-US-334-0133 VALENCE	Interim CSR[19]	Zeuzem *et al*. 2013[40]
GS-US-334-0123 PHOTON – 1	Sulkowski *et al.*2013 [41]	Interim CSR[42]
Phase II		
GS-US-334-0151 LONESTAR 2	Study protocol[43]	Lawitz *et al*. 2013c[44]
P2938-0721 QUANTUM	CSRs[45;46]	Lalezari *et al.* 2013[47]
11-1- 0258 SPARE	Osinusi *et al.* 2013[48]	Meissener *et al.* 2013[49;50] Nelson *et al*. 2013[51] Osinusi *et al* 2012[52]
P7977-0422 PROTON	Lawitz *et al.* 2013d[53]	CSR[54]
P7977-0523 ATOMIC	Kowdley *et al.* 2013[55]	Hassanien T *et al*. 2012[56]
P7977-0523 ELECTRON	Gane *et al.* 2013[57]	
P7977-0221 Dose ranging study	Rodriguez- Torres *et al*. 2013[58]	
GS-US-337-0118 LONESTAR	Lawitz *et al*. 2013e[59]	Lawitz *et al*. 2013 f[60]
GS-US-334-0126 (post-liver transplant)	Charlton *et al*. 2013[61]	
P7977-2025 (pre-liver transplant)	Curry *et al.* 2013[62]	
GS-US-334-0114 (Egyptian adults)	Ruane *et al.* 2013[63]	
NIAID SYNERGY Trial	Kohli *et al.* 2013[64]	
Sulkowski*	Sulkowski *et al* 2012[65]	
COSMOS*	Lawitz *et al.* 2013g[66]	Jacobson 2013c[67]
Compassionate use programme (Post –liver transplant)		
Not cited	Forns *et al*. 2013[68]	

*No study number. Please note that for Gilead studies where only conference poster/presentations were available and for which additional information was required to complete the following sections the relevant study protocol or clinical study report was used.

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.

Sofosbuvir has been studied in an extensive clinical trial programme covering all HCV genotypes (GT1–6), in a broad spectrum of patients representative of those seen in clinical practice. Patient populations studied included HCV treatment-naïve and treatment-experienced patients, those for whom current standard of care IFN-based regimens are unsuitable, special populations such as those with HIV co-infection and pre-liver transplant, and those with characteristics that have historically been associated with poor response to treatment such as cirrhosis, older age, high body mass index (BMI) and high baseline HCV viral loads.

Table 9: List of included RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Phase3				
Treatment naïve patients				
GS-US-334-0110 NEUTRINO	SOF 400 mg once daily (od)+PEG-IFN-2a administered via subcutaneous once weekly at a dose of 180 µg for 12 weeks + RBV administered orally twice daily with dose determined according to body weight (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg)	Not applicable	Patients with HCV GT1,4, 5 or 6 who had not received any previous treatment for HCV infection	Lawitz *et al*. 2013a[17]
P7977-123 FISSION	SOF 400 mg od+RBV administered orally in two daily doses according to body weight (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg) for 12 weeks	PEG-IFN-2a administered once weekly at a dose of 180 µg+RBV (800 mg daily in two divided doses) for 24 weeks	Patients with HCV GT2 or 3 who had not received any previous treatment for HCV infection	Lawitz *et al*. 2013a[17]
Treatment experienced patients				
GS-US-334-0108 FUSION	SOF 400 mg od+RBV administered orally twice daily with doses determined according to body weight (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg) for 12 weeks followed by 4 weeks of matching placebo	SOF 400 mg once daily+RBV administered orally twice daily with doses determined according to body weight (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg) for 16 weeks	Patients with HCV GT2 or 3 who had not had a response to prior treatment with an interferon-containing regimen	Jacobson *et al.* 2013a[18]
Patients unsuitable for interferon (e.g. interferon intolerant, ineligible or unwilling patients)				
POSITRON GS-US-334-0107	SOF 400 mg od+RBV administered orally twice daily with doses determined according to body weight (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body	Matching placebo for 12 weeks	Patients with HCV GT2 or 3 who had previously discontinued interferon therapy due to unacceptable adverse events	Jacobson *et al.* 2013a[18]

	weight of ≥ 75 kg) for 12 weeks		(interferon-intolerant), who had a concurrent medical condition precluding therapy with an interferon containing regimen (interferon-ineligible), or who had decided against treatment with an interferon-containing regimen (interferon-unwilling)	
Treatment naïve and experienced patients				
GS-US-334-0133 **VALENCE**	SOF 400 mg od+RBV administered orally twice daily with doses determined according to body weight (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg) for 12 weeks (GT2) or 24 weeks (GT3). All patients initially received 12 weeks treatment however emerging data suggested that GT3 patients would benefit from > 12 weeks of treatment and the study was amended and treatment extended to 24 weeks for GT3. Patients randomised to placebo were offered treatment in an alternative protocol.	Matching placebo for 12 weeks (GT2) or 24 weeks (GT3)	Patients with HCV GT2 or 3 who had never received treatment for HCV with interferon or who were either interferon intolerant or a interferon treatment failure	Interim CSR[19]
Patients co-infected with HIV				
GS-US-334-0123 **PHOTON 1**	<u>HCV GT1 Treatment naïve</u> SOF+RBV for 24 weeks <u>HCV GT2/3 Treatment naïve</u> SOF+RBV for 12 weeks <u>HCV GT2/3 Treatment experienced</u> SOF+RBV for 24 weeks Dosing was as follows for all groups: SOF 400 mg od+RBV administered orally twice daily with doses determined according to body weight (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg)	Not applicable	Patients with HCV GT1, 2 or 3 who were co-infected with HIV-1 and who were treatment-naïve (GT1,2 or 3) or treatment experienced (GT2 or 3)	Sulkowski *et al*. 2013[41]

PHASE 2				
GS-US-334-0151 **LONESTAR-2**	SOF 400 mg od+PEG-IFN-2a (subcutaneous 180 µg)+RBV administered orally twice daily with dose determined according to body weight (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg) for 12 weeks	Not applicable	Patients with HCV genotype 2 or 3 who had failed treatment with PEG and RBV therapy (treatment experienced)	Protocol[43]
P2938-0721 **QUANTUM**	GS-0938 (an experimental treatment) 300 mg od GS-0938+SOF 400 mg od GS-0938+SOF 400 mg od +RBV SOF 400 mg once daily +RBV Patients were randomised to receive treatment for 12 or 24 weeks	Placebo for 24 weeks	Patients with HCV GT1 who had not previously received treatment for HCV infection (Treatment naïve)	Interim CSR[45]
11-1-0258 (NIAID-Sponsored) **SPARE**	Two part trial Part 1 (Proof of concept – open label) SOF 400 mg od+RBV administered orally twice daily with dose determined according to body weight (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg) for 24 weeks Part 2 SOF 400 mg od+RBV (weight based) or low dose RBV (600 mg daily) for 24 weeks	Not applicable	Patients with HCV GT1 who had not previously received treatment for HCV infection (Treatment-naïve, difficult to treat patients)	Osinusi *et al.* 2013[48]
P7977-0422 **PROTON**	GT1 (Randomised cohort) SOF 200 mg or 400 mg, od for 12 week+PEG-IFN-2a (180 µg per week subcutaneously)+RBV (weight-based dosing: 1,000–1,200 mg daily). After week 12 SOF patients with an extended rapid virologic response (eRVR; HCV RNA < 15 IU/mL [LLOD]) from Weeks 4–12 received PEG-IFN+RBV for a further 12 weeks, whereas SOF patients without an eRVR received PEG+RBV for 36 weeks GT2 or 3 (Non-randomised open label) SOF 400 mg od+PEG 180 µg per week subcutaneously+RBV 1000 mg daily in patients with	GT1 Placebo+PEG-IFN-2a (180 µg per week)+RBV (1000 – 1200 mg daily) for 12 weeks followed by PEG (180 µg per week)+RBV (1000 – 1200 mg daily) for 36 weeks GT2/3 Not applicable	Patients with HCV GT1,2 or 3 who had not previously received treatment for HCV infection (Treatment naïve)	Lawitz *et al.* 2013d[53]

	a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg for 12 weeks			
P7977-0724 **ATOMIC**	SOF 400 mg od+PEG-IFN-2a 180 µg subcutaneously od and RBV 1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg for 12 weeks OR SOF 400 mg od+PEG-IFN-2a 180 µg subcutaneously od and RBV 1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg for 24 weeks OR SOF 400 mg od+PEG-IFN-2a 180 µg subcutaneously od and RBV 1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg followed by 12 weeks of either SOF monotherapy or SOF plus RBV	Not applicable	Patients with HCV GT 1,4,5 or 6 who had not previously received treatment for HCV infection (Treatment naïve)	Kowdley *et al*. 2013[55]
P7977-0523 **ELECTRON**	<u>Treatment naïve GT2/3</u> SOF 400 mg od for 12 weeks and PEG-IFN-2a 180 µg subcutaneously od for 0, 4, 8 or 12 weeks OR SOF 400 mg od monotherapy for 12 weeks OR SOF 400 mg od+PEG-IFN-2a 180 µg subcutaneously od+ RBV 1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg for 8 weeks <u>Treatment experienced GT1</u> SOF 400 mg od+RBV1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg for 12 weeks <u>Treatment naïve GT1</u> SOF 400mg od+RBV 1000 mg daily in patients with	Not applicable	Patients with HCV GT2 and 3 who had not previously received treatment for HCV infection (Treatment naïve). Patients with HCV GT1 who had not previously received treatment for HCV infection or who had had no response to prior treatment (Treatment naïve / Treatment experienced)	Gane *et al*. 2013[57]

	a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg for 12 weeks			
P7977-0221 **Dose ranging study**	SOF 100, 200 or 400 mg od, 180 µg subcutaneously od+RBV 1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg for 28 days followed by PEG-IFN-2a+RBV for a further 44 weeks	Placebo+PEG-IFN-2a + RBV for 28 days followed by PEG-IFN-2a+RBV for a further 44 weeks	Patients with HCV GT1 who had not previously received treatment for HCV infection (Treatment naïve)	Rodriguez-Torres M *et al.* 2013[58]
LONESTAR	Cohort A (Treatment naïve) • Fixed dose combination tablet containing SOF 400 mg od+ledipasvir 90 mg once daily for 8 weeks • Fixed dose combination tablet containing SOF 400 mg od+ledipasvir 90 mg od plus RBV(1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg) for 8 weeks • Fixed dose combination tablet containing SOF 400 mg od+ledipasvir 90 mg od for 12 weeks Cohort B (Failed a previous protease inhibitor regimen) • Fixed dose combination tablet containing SOF 400 mg od+ledipasvir 90 mg od for 12 weeks • Fixed dose combination tablet containing SOF 400 mg od+ledipasvir 90mg od plus RBV(1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg) for 12 weeks	Not applicable	Patients with HCV GT1 treatment naïve (cohort A) or who had failed a previous protease inhibitor regimen (cohort B).	Lawitz *et al.* 2013e[59]
GS-US-334-0126	SOF 400 mg od+ascending RBV starting at 400 mg/day (400 to 1,200 mg) for 24 weeks	Not applicable	Liver transplant patients with established recurrent HCV of any genotype	Charlton *et al*. 2013[61]

P7977-2025	SOF 400 mg od+RBV (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg) up to 48 weeks	Not applicable	Patients with HCV any genotype awaiting liver transplant	Curry *et al.* 2013[62]
GS-US-334-0114	SOF 400 mg od+RBV administered orally twice daily with dose determined according to body weight (1000 mg daily in patients with a body weight < 75 kg and 1200 mg daily in patients with a body weight of ≥ 75 kg) for 12 or 24 weeks	Not applicable	Patients of Egyptian ancestry with HCV GT4	Ruane *et al.* 2013[63]
NIAID SYNERGY	SOF 40mg od+ledipasvir 90 mg od GS-9669 500 mg od GS-9451 80 mg od	Not applicable	Patients with HCV who had not previously received treatment for HCV infection	Kohli *et al*. 2013[64]
Sulkowski	SOF 400 mg for 7 days then daclatasvir 60 mg od for 23 weeks SOF 400 mg od+daclatasvir 60 mg od for 24 weeks SOF 400 mg od+daclatasvir 60 mg od+RBV for 24 weeks	Not applicable	Patients with HCV GT1,2 or 3 who had not previously received treatment for HCV infection	Sulkowski *et al.* 2012[65]
COSMOS	SOF 400mg od+simeprevir 150 mg od for 12 or 24 weeks (+/-RBV)	Not applicable	Patients with HCV GT1 who were null responders to PEG-IFN + RBV	Lawitz *et al* 2013g[66]
Compassionate use programme (post liver transplant)				
Not known	SOF 400 mg od for ≤ 48 weeks with appropriate RBV doses±PEG-IFN at the physicians discretion	Not applicable	Patients with severe recurrent HCV following liver transplant including those with fibrosing cholestatic hepatitis	Forns *et al*.2013[68]

CSR – clinical study report; HCV – hepatitis C, GT – genotype; od –once daily; PEG IFN-2a – peginterferon alpha 2a; RBV – ribavirin; SOF - sofosbuvir

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.

The following studies compare sofosbuvir directly with the comparators specified in the scope and decision problem.

Study	Patient Group	Comparator and current standard of care
GS-US-334-0107 POSITRON	HCV GT2 or 3 interferon unsuitable	Placebo
P7977-123 FISSION	HCV GT2 or 3 treatment naïve	PEG+RBV
GS-US-334-0133 VALENCE	HCV GT2 or 3 treatment experienced group	Placebo

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.

The following studies have been excluded from further discussion:

- NIAID SYNERGY, COSMOS, LONESTAR and Sulkowski are excluded from further discussion on the basis they do not include relevant drug combinations and are outside of the scope.

- GS-US-334-0114 – study in patients of Egyptian ancestry. This study is ongoing and full results are not yet available.

- The compassionate use programme (post liver-transplant) and the post-liver transplant study [GS-US-334-0126]) are excluded as they are outside of the scope.

The main focus of the clinical section of this submission is on the five pivotal Phase 3 studies:

- GT1,4,5 and 6 – NEUTRINO

- GT2, 3 - FISSION, FUSION, POSITRON and VALENCE

In addition summary information is provided for:

- The Phase 2 studies (LONESTAR-2, QUANTUM, SPARE, PROTON, ATOMIC and ELECTRON). These were used to design of the Phase 3 studies and provide supportive information during the regulatory process. QUANTUM, PROTON, ATOMIC and ELECTRON also identified the once-daily dose of sofosbuvir to be taken forward into the Phase 3 programme and provided the first efficacy and safety data across different genotypes.

- Studies in HCV/HIV co-infected [PHOTON-1] and pre-liver transplant HCV patients [P7977-2025]

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). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Summary information on the pivotal Phase 3 sofosbuvir clinical trials (NEUTRINO FISSION, FUSION, POSITRON, VALENCE) are provided in Table 10 (Section 6.3.2).

The completed Phase 3 trials (NEUTRINO, FISSION, FUSION and POSITRON) have been published in the New England Journal of Medicine. The clinical study reports (CSRs) for each study have been used as a source for additional information where necessary. VALENCE is currently ongoing and the interim CSR[19] has been used to inform this submission supported by data from a recently published poster (Zeuzem *et al.* 2013)[40].

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.

Table 10: Comparative summary of methodology of the phase III RCTs

Trial no. **(acronym)**	**GS-US-334-0110** **NEUTRINO – GT1, 4, 5, 6 Treatment naïve patients** **(Lawitz *et al.* 2013a)[17]**	**P7977-1231** **FISSION – GT2, 3 Treatment naïve patients** **(Lawitz *et al.* 2013a)[17]**	**GS-US-334-0108** **FUSION – GT2,3 Treatment experienced patients** **(Jacobson *et al.* 2013a)[18]**	**GS-US-334-0107** **POSITRON – GT2, 3 Peginterferon intolerant, ineligible or unwilling patients** **(Jacobson *et al.* 2013a)[18]**	**GS-US-334-0133** **VALENCE – GT2, 3 Treatment naïve and experienced patients** **(CSR and Zeuzem *et al.* 2013)[19;40]**
Location	Multicentre 56 sites in the United States	Multicentre and multinational 97 sites in Australia, Italy, Netherlands, New Zealand, Sweden and United States	Multicentre and multinational 67 sites in Canada, New Zealand and the United States	Multicentre and multinational 63 sites in Australia, Canada, New Zealand and the United States	Multicentre 80 sites in Austria, Estonia, France, Germany, Italy, Netherland, Poland, Spain, Sweden and UK
Design	Single-group, open-label phase III study of SOF + PEG-IFN-2a + RBV	Randomised, open label, active-control phase III study comparing SOF + RBV for 12 weeks with PEG-IFN-2a +RBV for 24 weeks	Double-blind, active-controlled phase III study comparing SOF+RBV for 12 weeks with SOF+RBV for 16 weeks	Double-blind, placebo controlled phase III study comparing SOF + RBV with placebo	Multicentre, randomised, double-blind, placebo-controlled comparing SOF+RBV with placebo in treatment-experienced and treatment-naïve patients with HCV GT 2 or 3
Duration of study	Treatment duration = 12 Follow up = 12 weeks	Treatment duration = 12 or 24 weeks Follow up = 12 weeks	Treatment duration = 12 or 16 weeks Follow up = 12 weeks	Treatment duration = 12 weeks Follow up = 12 weeks	Treatment duration = 12 weeks (GT2) or 24 weeks (GT2 or 3) NOTE: The initial treatment duration for all patients was 12 weeks but following data from FUSION which indicated that patients with HCV GT3 would benefit from 12 weeks of treatment VALENCE was amended to allow 24 weeks of treatment for this GT3

					subgroup. At the time of the amendment 11 GT3 patients had already completed 12 weeks of treatment; the remaining 250 GT3 patients were treated for 24 weeks. All GT2 patients randomised to active treatment continued to receive SOF+RBV for 12 weeks and all placebo recipients were discontinued from the study and offered treatment with SOF+RBV under a separate protocol (Study GS-US-334-0109 Rollover Study)
Method of randomisation	Not applicable - single group study	Patients were randomised in a 1:1 ratio using a centralised system. Randomisation was stratified according to HCV GT (2 or 3), screening HCV RNA level (<6 $\log_{10}$ IU per millilitre or ≥ 6 $\log_{10}$ IU per millilitre), and the presence or absence of cirrhosis	Patients were randomised in a 1:1 ratio to one of the treatment regimens. Patients were randomised using an Interactive Web Response System. Randomisation was stratified according to the presence or absence of cirrhosis and HCV GT2 or 3 infection	Patients were randomised in a 3:1 ratio to receive SOF+RBV or placebo. Randomisation was stratified according to the presence or absence of cirrhosis	Patients were randomised in a 4:1 ratio to receive SOF+RBV (stratified according to GT) or matching placebo. Patients were randomised using an Interactive Web Response System
Method of blinding (care provider, patient and outcome assessor)	Not applicable – open label study	Not applicable – open label study	Patients and clinicians blinded to SOF treatment HCV RNA results were blinded to the investigator and sponsor except at screening. As such, independent monitoring was employed to assess for virological failure and the need for confirmatory HCV RNA samples.	Patients and clinicians blinded to SOF treatment HCV RNA results were blinded to the investigator and sponsor except at screening. As such, independent monitoring was employed to assess for virological failure and the need for confirmatory HCV RNA samples.	Patients and clinicians were initially blinded to SOF treatment

Intervention(s) (n =) and comparator(s) (n =)	SOF+PEG-IFN-2a+RBV n=327	SOF+RBV for 12 weeks n=256 PEG-IFN-2a+RBV for 24 weeks n=243	SOF+RBV for 12 weeks n=103 SOF+RBV for 16 weeks n=98	SOF+RBV n=207 Placebo n= 71	SOF+RBV n=334 (GT2 12 weeks n=73, GT3 12 weeks n=11, GT3 24 weeks n=250) Placebo n = 85
Primary outcomes	The proportion of patients with a SVR 12 weeks after discontinuation of therapy (SVR12 defined as an HCV RNA level below the lower limit of quantification at 12 weeks after the end of treatment). Pre-specified comparison to a historical control rate of 60% (as agreed with the FDA)	The proportion of patients with a SVR 12 weeks after discontinuation of therapy (SVR12 defined as an HCV RNA level below the lower limit of quantification at 12 weeks after the end of treatment).	The proportion of patients with a SVR 12 weeks after discontinuation of therapy (SVR12 defined as an HCV RNA level below the lower limit of quantification at 12 weeks after the end of treatment). Pre-specified comparison to a historical control rate of 25% (as agreed with the FDA)	The proportion of patients with a SVR 12 weeks after discontinuation of therapy (SVR12 defined as an HCV RNA level below the lower limit of quantification at 12 weeks after the end of treatment).	The proportion of patients with a SVR 12 weeks after discontinuation of therapy (SVR12) (defined as an HCV RNA level below the lower limit of quantification at 12 weeks after the end of treatment).
Secondary outcomes	• Proportion of patients who attain SVR at 4 weeks and 24 weeks after discontinuation of therapy (SVR4 and SVR24) • Absolute values and change from baseline in HCV-RNA during treatment and after treatment discontinuation • Rates of virological failures • Emergence of viral resistance to sofosbuvir during treatment and after treatment discontinuation	• Proportion of patients who attain SVR at 4 weeks and 24 weeks after discontinuation of therapy (SVR4 and SVR24) • Absolute values and change from baseline in HCV-RNA during treatment and after treatment discontinuation • Rates of virologic failure • Emergence of viral resistance to sofosbuvir during treatment and after treatment discontinuation	• Proportion of patients with HCV RNA < LLOQ (i.e., < 25 IU/mL) 12 weeks after discontinuation of therapy for the 12-week versus 16-week treatment groups • Proportion of patients who attained SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24) • Rates of virologic failure • Kinetics of circulating HCV RNA during treatment and after	• Proportion of patients who attain SVR at 4 weeks and 24 weeks after discontinuation of therapy (SVR4 and SVR24) • Kinetics of circulating HCV RNA during treatment and after treatment discontinuation, including virologic failure • Rates of virologic failure • Emergence of viral resistance to sofosbuvir during treatment and after treatment discontinuation	• Proportion of patients who attain SVR at 4 weeks and 24 weeks after discontinuation of therapy (SVR4 and SVR24) • Determination of efficacy of treatment with SOF+RBV based on prior treatment history • Kinetics of circulating HCV RNA during treatment and after treatment discontinuation, including virologic failure • Rates of virologic failure

			treatment discontinuation • Emergence of viral resistance to sofosbuvir during treatment and after treatment discontinuation		• Emergence of viral resistance to sofosbuvir during treatment and after treatment discontinuation
Exploratory outcomes	• Effect of treatment on health related quality of life using the SF-36, CLDQ-HCV, FACIT-F and WPAI quality of life questionnaire	• Effect of treatment on health related quality of life using the SF-36	• Effect of treatment on health related quality of life using the SF-36, CLDQ-HCV, FACIT- F and WPAI	• Effect of treatment on health related quality of life using the SF-36	• Effect of treatment on health related quality of life using the SF-36, CLDQ-HCV, FACIT- F and WPAI

CLDQ-HCV, Chronic Liver Disease Questionnaire – Hepatitis C, FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FDA, Food and Drugs Administration; HCV, hepatitis C; LLOQ, lower limit of quantitation; PEG-IFN-2a,peginterferon interferon alpha-2a; RBV,ribavirin; FF-3, short form 36; SOF, sofosbuvir; SVR,sustained virological response; WPAI, Work Productivity and Activity Impairement

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.

Summary details of the eligibility criteria for each phase III trial are provided in Table 11 with further details provided in Table 12. The key differences between the studies in terms of inclusion/exclusion criteria relate to the HCV genotype, degree of prior treatment experience and percentage of patients with cirrhosis included (Table 11).

Table 11 Summary eligibility criteria

	NEUTRINO	FISSION	FUSION	POSITRON	VALENCE
Genotype	GT1,4,5 or 6	GT2 or 3	GT2 or 3	GT2 or 3	GT2 or 3
Specific inclusion criteria	Treatment-naïve: no prior treatment with RBV or interferon (IFN)		Prior treatment failure with IFN-based therapy	Unsuitable for IFN (intolerant, contraindicated, unwilling)	Treatment naïve (no prior treatment with IFN) or treatment – experienced (either IFN intolerant or a treatment failure)
Cirrhosis permitted	Up to 20%		Up to 30%	Up to 20%	Up to 20%
General inclusion criteria	≥18 years of age; confirmation of CHC by positive anti-HCV, positive HCV RNA or positive HCV genotyping ≥6 months prior to baseline or liver biopsy with evidence of CHC; serum HCV RNA ≥104 IU/mL during screening; BMI ≥18 kg/m^2 (no upper limit to age or BMI)				
Exclusion criteria	Co-infection with HBV or HIV; any other clinically significant chronic liver disease (including HCC); history of consistent decompensated liver disease; history of major organ transplant; clinically relevant drug or alcohol abuse. Women who were pregnant or breastfeeding or men whose partners were pregnant.				

BMI, body mass index; CHC, chronic hepatitis C; GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; ribavirin, RBV; IFN, interferon

In POSITRON patients unsuitable for IFN were classified as IFN unwilling, IFN ineligible or IFN intolerant based on the following criteria (Jacobson *et al.* 2013a)[17]:

- IFN unwilling: patient had to have medical records documenting his/her decision declining treatment with an IFN-based regimen ≥ 3 months prior to signing the study informed consent

- IFN ineligible: patient was deemed ineligible by the investigator for treatment with IFN due to ≥1 of the following comorbidities, which are deemed at risk for worsening with IFN treatment:

    - Autoimmune disorders including but not limited to: dermatomyositis, immune (idiopathic) thrombocytopenic purpura, inflammatory bowel disease, interstitial lung disease, interstitial nephritis, polymyositis,

psoriasis, rheumatoid arthritis, sarcoidosis, and systemic lupus erythematosus
    - Significant psychiatric disease necessitating hospitalization or period of disability, or history of psychosis, schizophrenia, bipolar disorder, moderate depression, schizoaffective disorder, suicidal ideation, or suicide attempt
    - Seizure disorder
    - Poorly controlled thyroid dysfunction; hypothyroidism (thyroid-stimulating hormone ≥2 x the upper limit of normal [ULN] and ≤10 x ULN) or hyperthyroidism (thyroid-stimulating hormone < the lower limit of normal and >0.1 µIU/mL)
    - Retinal disease
    - Poorly controlled diabetes (haemoglobin [Hb] A1c >6.1% and ≤10%)
    - Other relative IFN contraindications, including age, which are not specifically listed above, but may have been approved after discussion with the Gilead Medical Monitor
- IFN intolerant: patient completed ≤12 weeks of treatment (ending ≥3 months prior to Screening) with IFN and discontinued treatment due to development or significant worsening of ≥1 of the following conditions:
    - Significant local or systemic adverse reaction to IFN (e.g. hypersensitivity and injection-site reactions)
    - Psychiatric disease necessitating hospitalization or period of disability, or psychosis, schizophrenia, bipolar disorder, depression, schizoaffective disorder, suicidal ideation, or suicide attempt
    - Significant cognitive impairment
    - Neuropathy
    - Disabling flu-like symptoms (e.g. arthralgias, fatigue, pyrexia, and myalgia)
    - Gastrointestinal toxicity with nausea, vomiting, or diarrhoea
    - Thrombocytopenia (platelets <25,000/µL)
    - Neutropenia (absolute neutrophil count <500/µL)
    - Development of colitis, nonalcoholic pancreatitis, or ophthalmologic disorders
    - Autoimmune disorder including but not limited to: myositis, hepatitis, inflammatory bowel disease, interstitial lung disease, interstitial nephritis, immune (idiopathic) thrombocytopenic purpura, psoriasis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, and thyroiditis
    - Adverse event related to IFN that was not listed following consultation with the Gilead Medical Monitor

In VALENCE patients classed as treatment experienced were defined as follows (VALENCE Interim CSR)[19]:

- IFN intolerant - defined as above for POSITRON
- IFN ineligible - defined as above for POSITRON
- Treatment failure defined as a subject with documented prior treatment failure with 12 ≥ weeks IFN with or without RBV. The subjects medical records must have included sufficient detail of prior therapy with IFN (start/stop dates and viral response) to allow for categorization of prior response as either:

- Non-response: Subject did not achieve undetectable HCV RNA levels on treatment
- Relapse/breakthrough: Subject achieved undetectable HCV RNA during treatment or within 4 weeks after treatment

Table 12: Eligibility criteria in the RCTs

Trial no. (acronym)	Key inclusion criteria	Key exclusion criteria

GS-US-334-0110 NEUTRINO
 	
Lawitz *et al.* 2013a[17]
	• ≥ 18 years of age
	• Infected with HCV GT1, 4, 5, or 6, documented by either positive anti-HCV antibody test, positive HCV RNA or positive HCV genotyping test ≥ 6 months prior to the Baseline/Day 1 visit, or a liver biopsy performed prior to the Baseline/Day 1 visit with evidence of chronic HCV infection
	• Serum HCV RNA levels ≥ 10,000 IU/mL during screening
	• Cirrhosis was permitted in approximately 20% of patients. Evidence of cirrhosis was defined as:
	• Liver biopsy showing cirrhosis
	  ○ Transient elastography (Fibroscan) showing cirrhosis or results >12.5 kPa
	  ○ A FibroTest® score of >0.75 and an APRI of >2 during screening
	  ○ In the absence of definitive diagnosis a liver biopsy was required
	• Undergone no prior treatment for HCV with IFN or RBV
	• BMI ≥ 18 kg/m^2
	• Liver imaging within 6 months of Baseline/Day 1 to exclude HCC
		• Received prior treatment for HCV with an IFN or RBV
		• Prior exposure to a direct-acting antiviral agents targeting the HCV NS5B polymerase
		• Co-infected with HBV or HIV
		• Chronic liver disease of a non-HCV aetiology
		• History of clinical hepatic decompensation
		• Had autoimmune disorders, psychiatric conditions, a history of solid organ transplant, or had clinically relevant drug or alcohol abuse within 12 months of screening.
		• Women who were pregnant or breastfeeding or men whose partners were pregnant.

P7977-1231 FISSION
 	
Lawitz *et al.* 2013a[17]
	• 18 years of age or older, or the legal age of consent, whichever was older, at screening
	• Chronic HCV GT2 or GT3 infection, documented by ≥ 1 serum HCV RNA level ≥10,000 IU/mL during screening and ≥ 1 of:
	  ○ positive anti-HCV antibody and HCV RNA tests ≥ 6 months prior to the Baseline/Day 1 visit and at screening, as well as a positive HCV genotyping test ≥ 6 months prior to the Baseline/Day 1 visit
	  ○ positive anti-HCV antibody and HCV RNA tests at screening and a liver biopsy with evidence of chronic HCV infection
	• Cirrhosis was permitted in approximately 20% of patients. Evidence
		• Co-infected with HBV or HIV
		• History of any other clinically significant chronic liver disease
		• History of consistent decompensated liver disease
		• History or current evidence of psychiatric conditions, immunological disorders, or major organ transplant with an existing functional graft, or had active substance abuse.
		• Women who were pregnant or breastfeeding or men whose partners were pregnant

	of Childs A cirrhosis was defined as: • Liver biopsy showing cirrhosis • Transient elastography, where locally approved, showing cirrhosis or results >12.5 kPa • A FibroSure® score of >0.75 and an APRI of >2 during screening • In the absence of definitive diagnosis a liver biopsy was required • Undergone no prior treatment for HCV, including but not limited to immunomodulatory and nucleoside/nucleotide treatments. • BMI ≥ 18 kg/m^2	

GS-US-334-0108 FUSION
 	
Jacobson *et al.* 2013a[18]
	• ≥ 18 years of age
	• Chronic HCV GT2 or GT3 infection, documented by HCV RNA level ≥10,000 IU/mL during screening and either:
	  ○ a positive anti-HCV antibody test, a positive HCV RNA test or a positive HCV genotyping test ≥ 6 months prior to the Baseline/Day 1 visit; or
	  ○ a liver biopsy prior to the Baseline/Day 1 visit with evidence of chronic HCV infection
	• Prior treatment failure with ≥ 12 weeks of treatment with IFN (pegylated, nonpegylated, or alfacon-1), either with or without RBV. Medical records had to be sufficient in detail to allow categorisation of failure as either non-response or relapse/breakthrough
	• Compensated cirrhosis was permitted in approximately 30% of patients. Evidence of cirrhosis was defined as:
	• Liver biopsy showing cirrhosis
	• Fibroscan, where locally approved, showing cirrhosis or results >12.5 Pa
	• A FibroTest® score of >0.75 and an APRI of >2 during screening
	• In the absence of definitive diagnosis a liver biopsy was required
	• Liver imaging within 6 months of baseline/day 1 to exclude HCC was required in patients with cirrhosis.
	• BMI ≥ 18 kg/m^2
		• Prior exposure to a direct-acting antiviral targeting the HCV NS5B polymerase
		• Co-infected with HBV or HIV
		• Chronic liver disease of a non-HCV aetiology
		• History or current evidence of clinical hepatic decompensation
		• History of solid organ transplant,
		• Clinically relevant substance abuse within 12 months of screening.
		• Women who were pregnant or breastfeeding or men whose partners were pregnant

GS-US-334-0107 POSITRON	• ≥ 18 years of age • Chronic HCV GT2 or GT3 infection, documented by HCV RNA level	• Prior exposure to a direct-acting antiviral targeting the HCV NS5B polymerase

Jacobson *et al.* 2013a[18]	≥ 10,000 IU/mL during screening and either: ○ a positive anti-HCV antibody test, a positive HCV RNA test or a positive HCV genotyping test ≥ 6 months prior to the Baseline/Day 1 visit; or ○ a liver biopsy prior to the Baseline/Day 1 visit with evidence of chronic HCV infection • Patients had to be either: • IFN unwilling: patient had to have medical records documenting his/her decision declining treatment with an IFN-based regimen ≥3 months prior to signing the Informed Consent • IFN ineligible: assessed by the investigator as having ≥1 of a number of pre-specified co-morbidities, which were deemed at risk for worsening with IFN treatment • IFN intolerant: patient completed ≤12 weeks of treatment with IFN (ending ≥3 months prior to screening) and discontinued treatment due to development or significant worsening of ≥1 of a number of pre-specified conditions including significant local or systemic AEs to IFN • Compensated cirrhosis was permitted in approximately 20% of patients. Evidence of cirrhosis was defined as: • Liver biopsy showing cirrhosis • Fibroscan, where locally approved, showing cirrhosis or results >12.5 kPa • A FibroTest® score of >0.75 and an APRI of >2 during screening • In the absence of definitive diagnosis a liver biopsy was required • Liver imaging within 6 months of baseline/day 1 to exclude hepatocellular carcinoma was required in patients with cirrhosis. • BMI ≥ 18 kg/m^2	• Co-infected with HBV or HIV • Chronic liver disease of a non-HCV aetiology • History or current evidence of clinical hepatic decompensation • History of solid organ transplant, • Clinically relevant substance abuse within 12 months of screening. • Women who were pregnant or breastfeeding or men whose partners were pregnant
GS-US-334-0133 VALENCE **Interim CSR**[19]	• Age ≥18 with chronic GT2 or GT3 HCV infection • HCV RNA >10,000 IU/mL at screening • Patients must be treatment-naïve (had never received treatment for HCV with IFN) or treatment-experienced (either IFN intolerant or a treatment failure) • Cirrhosis was permitted in approximately 20% of patients.	• Prior exposure to a direct-acting antiviral targeting the HCV NS5B polymerase • Pregnant or nursing female or male with pregnant female partner • Co-infected with HBV or HIV • Chronic liver disease of a non-HCV aetiology

	Determination of cirrhosis (by any of the following methods): • Presence of cirrhosis: positive liver biopsy, fibroscan >12.5kPa, or FibroTest® score >0.75 AND an APRI of >2 performed during screening • Absence of cirrhosis: negative liver biopsy, fibroscan ≤12.5kPa within ≤6 months of Baseline/Day 1, or FibroTest® score ≤0.48 AND an APRI of ≤1 performed during screening • BMI≥18kg/m^2 • Healthy according to medical history and physical examination with the exception of HCV diagnosis • Agree to use contraception for the duration of the study and 6 months after the last dose of study medication	• History or current evidence of clinical hepatic decompensation • HCC or other malignancy (with exception of certain resolved skin cancers) • History of clinically significant haemoglobinopathy, drug/alcohol abuse, solid organ transplantation, pulmonary disease, significant cardiac disease or porphyria • Chronic use of immunosuppressive agents or immunomodulatory agents • History or current evidence of any condition, prohibited concomitant therapy, laboratory abnormality or other circumstance that might interfere with treatment, assessment, or compliance with study protocol

APRI,aspartate to transaminase to platelets ratio index; BMI, body mass index; GT, genotype; HBV, hepatits B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN,interferon; RBV:ribavirin; RNA, ribonucleic acid

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.

6.3.4.1 Treatment naïve patients – NEUTRINO and FISSION

NEUTRINO – *HCV* GT1, 4, 5 or 6 treatment naive

Details of the patient characteristics at baseline are provided in Table 13. Patients had a mean age of 52 years and the majority were male (64%). Seventeen per cent (17%) were black and 14% Hispanic/ Latino. The proportions of patients with the different HCV genotypes were 89% GT1, 9% GT4, and 2% GT5 or 6, a distribution that is consistent with the prevalence of HCV genotypes in England where GT1 is the predominant genotype (46%). The study included a high proportion of patients with negative predictors of response to IFN-based therapy: 82% had a high baseline viral load (HCV RNA ≥800,000 IU/mL), 17% of the patients were black and 17% had cirrhosis. In addition, over 70% of patients had a non-CC IL28B genotype; the absence of two CC alleles in the IL28B gene being associated with reduced response to IFN-based therapy.

Table 13: NEUTRINO - Characteristics of participants (Lawtiz et al. 2013a)[17]

Characteristic	NEUTRINO
	SOF+PEG-INF-2a+RBV for 12 weeks
	(N = 327)
Mean age — yr (range)	52 (19–70)
Mean BMI (range)	29 (18–56)
Male — no. (%)	209 (64)
Self-reported race or ethnic group, n (%)†	
White	257 (79)
Black	54 (17)
Asian	7 (2)
Other	9 (3)
Hispanic or Latino	46 (14)
HCV GT, N (%)‡	
1a	225 (69)
1b	66 (20)
2	0
3	0
4	28 (9)
5	1 (<1)
6	6 (2)
Mean HCV RNA — $\log_{10}$ IU/ml	6.4±0.7
HCV RNA ≥800,000 IU/ml — no. (%)	267 (82)
IL28B genotype, n (%)	
CC	95 (29)
CT	181 (55)
TT	51 (16)

Missing data	0
Cirrhosis — no. (%)**	54 (17)
Alanine aminotransferase >1.5×ULN — no. (%)	166 (51)

BMI,body mass index;GT, genotype; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; ULN, upper limit of normal.

†Patients could choose more than one race or ethnicity category. ‡One patient counted as genotype 1a had a mix of genotype 1a and 1b.

** Hepatic cirrhosis was considered present when any one of the following was found: a liver biopsy sample showing cirrhosis; transient elastography (FibroScan) identifying cirrhosis or liver stiffness > 12.5 kPa; a serum FibroTest score > 0.75 (on a scale of o to 1) and an APRI > 2 during screening.

FISSION – HCV GT2 or 3 treatment naive

Details of the patient characteristics at baseline are provided in Table 14. The trial was designed to enrol patients with GT3 versus GT2 infection in a 3:1 ratio. This was achieved with 71% and 72% of patients having HCV GT3 infection in the SOF + RBV and PEG-IFN-2a + RBV groups, respectively. Three patients were originally classified as having GT1 infection on deep-sequencing analysis after randomization were excluded from the efficacy analysis but included in the safety analysis as reported by Lawitz *et al.* (2013a)[17]. Subsequent full sequencing showed these patients to have recombinant GT2/1 infection and these patients were therefore included in a revised analysis of SVR12 rates. The revised analysis including these three patients were submitted for licensing approval and are presented in the product SmPC (Appendix 1.0).

The demographics and baseline characteristics of the patients were balanced between the study groups. Cirrhosis was present in 20% of the patients in the SOF + RBV group and 21% of the patients in the PEG-IFN-2a + RBV group.

Table 14: FISSION - Characteristics of participants (Lawtiz *et al*. 2013a)[17]

Characteristic	FISSION	
	SOF+RBV for 12 weeks	PEG-IFN-2a+RBV for 24 weeks
	(N=256)	(N=243)
Mean age — yr (range)	48 (20-72)	48 (19-77)
Mean BMI (range)	28 (17-51)	28 (19-52)
Male — no. (%)	171 (67)	156 (64)
Self-reported race or ethnic group, n (%)†		
White	223 (87)	212 (87)
Black	12 (5)	5 (2)
Asian	14(5)	15 (6)
Other	7 (3)	11 (5)
Hispanic or Latino	41 (16)	31 (13)
HCV GT, N (%)		
1a	2(1)*	0
1b	1 (<1)*	0
2	70 (27)	67 (28)
3	183 (71)	176 (72(
4	0	0
5	0	0
6	0	0

Mean HCV RNA — log_{10} IU/ml	6.0±0.8	6.0±0.8
HCV RNA ≥800,000 IU/ml — no. (%)	145(57)	157 (65)
IL28B genotype, n (%)		
CC	108 (42)	106 (44)
CT	121 (47)	98 (40)
TT	25 (10)	38 (16)
Missing data	2 (1)	1 (<1)
Cirrhosis — no. (%)**	50 (20)	50 (21)
Alanine aminotransferase >1.5×ULN — no. (%)	138 (54)	146 (60)

BMI,body mass index; GT, genotype; HCV, hepatitis C virus; PEG-IFN-2a,pegylated interferon alpha 2a, RBV, ribavirin, RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; ULN, upper limit of normal.

†Patients could choose more than one race or ethnicity category

*Three patients were originally classified as having GT1 infection on deep-sequencing analysis after randomization were excluded from the efficacy analysis but included in the safety analysis As reported by Lawitz *et al*). Subsequent full sequencing showed these patients to have recombinant GT2/1 infection and these patients were therefore included in a revised analysis of SVR12 rates. The revised analysis including these three patients were submitted for licensing approval and are presented in the product SmPC (Appendix 1.0)

** Hepatic cirrhosis was considered present when any one of the following was found: a liver biopsy sample showing cirrhosis; transient elastography (FibroScan) identifying cirrhosis or liver stiffness > 12.5 kPa; a serum FibroTest score > 0.75 (on a scale of 0 to 1) and an APRI > 2 during screening.

6.3.4.2 HCV GT2 or 3 treatment experienced – FUSION

Details of the patient characteristics at baseline are provided in Table 15. The treatment groups were well balanced. Patients had a mean age of 54 years, the majority were male (86-71%) and white (85-88%). GT3 infection was present in 62% of the 12-week group and 64% of the 16-week group. Cirrhosis was present in 35% of the 12-week group and 33% of the 16-week group. Approximately 75% of those previously treated had either a virological breakthrough during prior treatment or virologic relapse after the end of treatment; the remainder did not have a response to treatment.

Three patients in each group were originally classified as having GT1 infection on deep-sequencing analysis after randomisation and were excluded from the original efficacy analysis but were included in the safety analysis (as reported by Jacobsen et al). Subsequent full sequencing showed these patients to have recombinant GT2/1 infection and these patients were therefore included in a revised analysis. The revised analyses including these 6 patients were submitted for licensing approval and are presented in the product SmPC (Appendix 1.0).

Table 15: FUSION - Characteristics of participants (Jacobson et al. 2013a)[18]

	FUSION	
Characteristic	**SOF+RBV 12 weeks n=103**	**SOF+RBV 16 weeks N=98**
Mean age (years)	54	54
Range	30–69	24–70
BMI, kg/m^2		
Mean	28	29
Range	19–43	20–44
Male sex — no. (%)	73 (71)	67 (68)
Self reported race or ethnicity†		
White	88 (85)	86 (88)
Black	5 (5)	1 (1)
Asian	7 (7)	5 (5)
Other	3 (3)	6 (6)
Hispanic or Latino		
Yes	10 (10)	8 (8)
No	93 (90)	89 (91)
HCV GT – n (%)		
1§	3 (3)	3 (3)
2	36 (35)	32 (33)
3	64 (62)	63 (64)
HCV RNA		
Mean — $\log_{10}$ IU/ml	6.5±0.67	6.5±0.63
≥800,000 IU/ml — no. (%)	80 (78)	77 (79)
IL28B genotype – no (%)		
CC	31 (30)	30 (31)
CT	53 (51)	56 (57)
TT	19 (18)	12 (12)
Cirrhosis — no. (%)	36(35)	32(33)
Baseline ALT >1.5× ULN — no. (%)	63(61)	56 (57)
Response to previous treatment		
Non response	25(24)	25(26)
Relapse	78(76)	73(74)

ALT, alanine aminotransferase; BMI, body mass index; GT, genotype; HCV, hepatitis C virus;SOF,sofosbuvir;: RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; ULN, upper limit of normal.

†Patients could choose more than one race or ethnicity category

§These patients were found to have GT1 infection by deep sequencing after randomisation, were excluded from the efficacy analysis but not from the safety analysis

6.3.4.3 HCV GT2 or 3 treatment naïve and experienced, IFN unsuitable- POSITRON[18]

Details of the patient characteristics at baseline are provided inTable 16. The distribution of patients based on the classification that IFN was not an option (IFN unwilling, IFN ineligible or IFN intolerant) was similar between the treatment groups. The most common reasons for ineligibility were clinically significant psychiatric disorders (57%) and autoimmune disorders (19%) and diabetes (5%). The most common adverse events leading to IFN-intolerance were disabling 'flu-like symptoms (32%), psychiatric disease (20%), thrombocytopenia (16%), and local/systemic adverse reactions (12%). Patients who are unsuitable to receive treatment with IFN-based regimens represent an important patient group as they currently have no treatment options.

Table 16: POSITRON - Characteristics of participants (Jacobson et al. 2013a)[18]

	POSITRON	
Characteristic	**Placebo n=71**	**SOF+RBV 12 weeks n=207**
Mean age (years)	52	52
Range	28–67	21–75
Body mass index, kg/m^2		
Mean	28	28
Range	20–43	18–53
Male sex — no. (%)	34 (48)	117 (57)
Race or ethnicity†		
White	66 (93)	188 (91)
Black	4 (6)	9 (4)
Asian	1 (1)	7 (3)
Other	0	3 (1)
Hispanic or Latino		
Yes	11 (15)	19 (9)
No	60 (85)	188 (91)
HCV genotype – n (%)		
1	0	0
2	34 (48)	109 (53)
3	37 (52)	98 (47)
HCV RNA		
Mean — $\log_{10}$ IU/ml	6.3±0.76	6.3±0.77
≥800,000 IU/ml — no. (%)	55 (77)	150 (72)
IL28B genotype – no (%)		
CC	29 (41)	97 (47)
CT	36 (51)	84 (41)
TT	6 (8)	26 (13)
Cirrhosis — no. (%)	13(18)	31(15)
Baseline ALT >1.5× ULN — no. (%)	42(59)	117(57)
Interferon classification – no (%)		
Contraindication	33(46)	88(43)
Unacceptable side effects	8(11)	17(8)

Patient's decision	30(42)	102 (49)
Response to previous treatment		
Non response	2(3)	2(1)
Relapse	4(6)	11 (5)

ALT, alanine aminotransferase; BMI,body mass index; HCV, hepatitis C virus; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; ULN, upper limit of normal.
†Patients could choose more than one race or ethnicity category

6.3.4.4 HCV GT2 or 3 treatment naïve and experience - VALENCE

Details of the patient characteristics at baseline are provided in Table 17

Table 17: VALENCE - Patient characteristics of participants in VALENCE (Interim CSR and Zeuzem et al. 2013) [19;40]

Characteristic	Placebo (N=85)	GT2 SOF+RBV 12 weeks (N=73)	GT3 SOF+RBV 12 weeks (N=11)	GT3 SOF+RBV 24 weeks (N=250)
Mean age, year (range)	49 (19-72)	58 (28-74)	46 (30-59)	48 (19-69)
Mean BMI, kg/m^2 (range)	26 (18-40)	26 (20-35)	28 (20-44)	25 (17-41)
Male, %	58	55	55	62
White, %	95	89	100	94
HCV GT, %				
GT2	XX	XXX	X	X
GT3	XX	X	XXX	XXX
Mean HCV RNA, log_{10} IU/mL	6.5	6.5	6.2	6.3
IL28B GT, %				
CC	26	33	36	34
CT	58	56	36	52
TT	17	11	27	13
Cirrhotic liver, %	21	14	18	23
ALT >1.5 x ULN, %	XX	XX	XX	XX
Prior HCV treatment-experienced, %	59	56	82	58
IFN intolerant, as % of experienced	0	7	0	7
Non-response, as % of experienced	36	24	44	28
Relapse/breakthrough, as % of experienced	64	68	56	65
Prior HCV treatment-naive, %	XX	XX	XX	XX
IFN eligible, as % of naive	XX	XX	XXX	XX

ALT, alanine aminotransferase; BMI, body mass index; GT, genotype; HCV, hepatitis C virus; IFN, interferon; RBV, ribavirin; RNA, ribonucleic acid; SOF, :sofosbuvir; ULN, upper limit of normal.

† Based on safety analysis set (same as full analysis set for active treatment groups).

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 18: Primary and secondary outcomes of the Phase 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
GS-US-334-0110 NEUTRINO (Lawitz et al. 2013a and InterimCSR)[17;69]	Sustained virological response SVR defined as an HCV RNA level below the lower limit of quantification 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 the EMA and FDA. SVR 12 is specified in the scope as an valid endpoint	<u>Secondary outcomes</u> • The proportion of patients who attain SVR4 and SVR24 • The kinetics of circulating HCV RNA during treatment and after treatment discontinuation determined. HCV RNA level was measured with the COBAS Taman HCV test with a lower limit of quantification of 25 IU per millilitre. • The emergence of viral resistance to sofosbuvir during treatment and after treatment discontinuation assessed by deep sequencing assays to characterize virological resistance. <u>Exploratory outcomes</u> Health related quality of life as	<u>Secondary outcomes</u> • 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 the EMA and FDA. • The kinetics of circulating HCV RNA during treatment part of routine clinical practice with current treatments (PEG, RBV, boceprevir and telaprevir) and is used to monitor and guide treatment (referred to as response guided therapy). • Deep sequencing refers to the number of times a nucleotide is read during the sequencing process and increases the sequencing accuracy by
P7977-1231 FISSION (Lawitz et al.				

2013a and interim CSR)[17;70]			assessed using SF-36, CLDQ-HCV, FACIT-F and WPAI; Hepatitis C	sequencing individual genomes a large number of times to determine low-frequency mutations. It is accepted by the most regulatory authorities as a valid method for characterising low frequency mutations. <u>Exploratory outcomes</u> • All QoL questionnaires are recognised and validated questionnaires
GS-US-334-0108 FUSION (Jacobson et al 2013 a and Interim CSR)[18;71]				
GS-US-334-0107 POSITRON (Jacobson et al 2013 a and Interim CSR)[18;72]				
GS-US-334-0133 VALENCE (Interim CSR)[19]				

CLDQ-HCV, Chronic Liver Disease Questionnaire; EMA, European Medicines Agency, FDA, Foods and Drusg Administration; HCV, Hepatitis C; HCV; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; QoL, quality of life; SF-36 , Short Form—36 Items; SVR, sustained virological response, WPAI, Work Productivity and Activity Impairment.

NOTE: Historically, SVR rate 24 weeks after treatment cessation (SVR24) has been used as an endpoint for HCV studies to determine efficacy. However, SVR rate 12 weeks after treatment cessation (SVR12) has been shown to have high concordance with SVR24 rates, based on clinical trial data of various treatment regimens and durations. As such, SVR12 has been established as an appropriate endpoint for regulatory approval and is now accepted by most clinical and regulatory authorities (including the FDA and EMA). High concordance between SVR12 and SVR24 in sofosbuvir-based therapy has also been demonstrated in the Phase 3 trials NEUTRINO, FISSION, FUSION and POSITRON, with 99% of patients who achieved SVR12 also achieving SVR24 (Yoshida *et al.* 2013)[39]. As a result, SVR12 is an appropriate endpoint for the sofosbuvir trials reported herein and is directly comparable with historical SVR24 endpoints reported in the literature for comparator treatments.

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 19 Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
GS-US-334-0110 NEUTRINO (Lawitz *et al*. 2013a and interim CSR)[17;69]	The hypothesis was that patients treated with SOF+PEG-IFN-2a and RBV for 12 weeks would have a rate of sustained virologic response at 12 weeks (SVR12) after treatment >60%. The basis for this 60% SVR null rate was based on: a historical SVR rate of ~65% calculated from the telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data after adjusting for the expected proportion of patients	*Primary analyses of the primary outcome* The primary endpoint was tested using a two-sided one-sample binomial test to determine if a 60% rate could be ruled out at the 0.05 significance level. *Secondary analyses of the primary efficacy outcome* Pre-specified sub-group analyses of SVR12 were also performed for various pre-specified demographic and baseline clinical characteristics.	It was determined that a planned sample size of 300 patients would provide a power of 90% to show a rate SVR with the SOF regimen was higher that the historical rate of 60% after adjustment of the presence of cirrhosis and expected safety benefit. The expectation of higher response rates, improved safety and shorter treatment duration led to a joint decision with the regulatory authorities not to include a currently available	Primary analysis of the primary outcome was determined in the FAS population. Values for missing data were not imputed for any endpoint with the exception of HCV RNA and health-related quality of life (HRQoL) data. For categorical HCV RNA data, if a data point was missing, and was preceded and followed by values that were deemed successes (i.e. HCV RNA <LLOQ), then the missing data point was termed a success; otherwise the data point was termed as a failure (i.e. HCV RNA ≥LLOQ). Patients with missing data due to premature discontinuation of the

	with cirrhosis (~20%) in NEUTRINO[1], and a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment.	In addition, pre-specified multivariate logistic-regression analyses were performed to characterise the relationship between SVR and these characteristics. A stepwise selection procedure was used to identify independent predictors of SVR, with p=0.10 as the threshold level for variables to be entered into the final model and p=0.05 for those to be retained in the final model. All demographic and baseline clinical factors delineated in a univariate logistic regression model were candidate variables for inclusion in the multivariate model using the stepwise procedure described above.	protease-inhibitor regimen as an active control.	study had missing data imputed up to the time of their last dose (for on treatment displays). If study days associated with the last dosing date was greater than the lower bound of a visit window, and the value at the visit was missing, then the value was imputed. If the study days associated with the last dosing date were less than the lower bound of a visit window then the on-treatment value at that visit remained missing. If no HCV RNA values were obtained after the last dose of study drug, the subject was considered a treatment failure for SVR endpoints. For continuous HCV RNA data if a data point was missing, and was preceded and followed by values that were deemed successes (i.e. HCV RNA <LLOQ), then the missing data point was termed a success; otherwise the data point was termed as a failure (i.e. HCV RNA ≥LLOQ). No other imputation was performed. For HRQoL data, missing data at on-treatment visits and post-treatment Week 4 were not imputed. The last observation was used for imputation of

[1] The weighted average of the telaprevir and boceprevir data was estimated to be ~70% in non-cirrhotic patients and 44% in cirrhotic patients. The SVR rate for the historical control in this study (i.e. a patient population of 80% non-cirrhotics and 20% cirrhotics) was then calculated to be ~65% (i.e. 0.8 x 70% + 0.2 x 44%). A 5% trade-off in efficacy was exchanged for an expected improved safety profile and shorter duration of treatment and, therefore, the historical SVR rate used for comparison in NEUTRINO was 60%.

				missing data at post-treatment visits after the post-treatment Week 4 visit because patients with confirmed HCV RNA >LLOQ at the post-treatment Week 4 visit were not required to return for subsequent post-treatment visits.
P7977-1231 FISSION (Lawitz *et al*. 2013a and Interim CSR)[17;70]	The study hypothesis was that SOF+RBV administered for 12 weeks would be non-inferior to PEG-IFN-2a+RBV administered for 24 weeks.	*Primary analyses of the primary outcome* Using a closed testing procedure, the noninferiority of SOF+RBV relative to PEG-IFN-2a+RBV for SVR12 (primary efficacy endpoint) was tested first. Noninferiority was demonstrated if the lower bound of the 2-sided 95% confidence interval on the difference in SVR12 rates (SOF+RBV group minus PEG-IFN-2a+RBV group) was > –15%. The estimate and 95% CI on the difference between groups in SVR12 rates was constructed based on stratum-adjusted Mantel-Haenszel (MH) proportions for the assessment of noninferiority. If noninferiority was established, then the superiority of SOF+RBV relative to PEG-IFN-2a+RBV was tested using a Cochran-Mantel-Haenszel (CMH) test statistic for stratified proportions. Superiority was demonstrated if the 2-sided p-value associated with the test of superiority was < 0.05.	It was determined that a sample size of 250 patients with HCV GT 2 or 3 in each study group would provide at least 90% power to detect a 12% difference between groups for SVR using a two-sided chi-square test at the 0.05 significance level, and assuming an SVR rate of 75% in the control arm with HCV GT 2 or 3 in each treatment group provided a power of more that 95% to established the non inferiority of SOF+RBV and ribavirin, as compared with -IFN-2a+RBV	The full analysis set (FAS) included subjects with GT2, 3, or mixed 2/3 HCV infection who were randomised into the study and received at least 1 dose of study medication. Values for missing data were not imputed for any endpoint with the exception of HCV RNA data. Methods for handling missing data were as reported above for NEUTRINO. Subjects who did not have an assessment of cirrhosis performed at screening as required by the protocol were considered to be noncirrhotic for the purposes of the subgroup analyses and for stratified statistical tests unless an assessment of cirrhosis was made during the treatment or post- treatment period and the subject was determined to have cirrhosis.

		Secondary analyses of the primary outcome Exploratory sub-group analyses of SVR12 were also performed for various pre-specified demographic and baseline clinical characteristics. In addition, pre-specified exploratory multivariate logistic-regression analyses were performed to characterise the relationship between SVR and these characteristics. A stepwise selection procedure was used to identify independent predictors of SVR, with p=0.10 as the threshold level for variables to be entered into the final model and p=0.05 for those to be retained in the final model. All demographic and baseline clinical factors delineated in a univariate logistic regression model were candidate variables for inclusion in the multivariate model using the stepwise procedure described above.		
GS-US-334-01018 FUSION (Jacobson *et al*. 2013 a and Interim CSR)[18;71]	The hypothesis being tested was that the proportions of patients with an SVR12 in both treatment groups were greater that a historical control rate of 25%.	The secondary analysis of comparing the SVR rates in the 12- and 16-week treatment arms was performed using a Cochran-Mantel-Haenszel test stratified by the randomisation stratification factors.	It was calculated that a sample size of 100 patients in each group would provide >97% power to detect ≥20% improvement in SVR12 rate from a historic control rate of 25% using 2-sided exact 1-sample	The full analysis set included subjects with genotype 2 or 3 HCV infection who were randomised into the study and received at least 1 dose of study drug. Primary analysis of the primary outcome was performed in the FAS population.

		Subgroup analyses of SVR12 were also performed for various pre-specified demographic and baseline clinical characteristics. Multivariate logistic-regression analyses involving treatment regimens and prespecified baseline characteristics and demographics were performed to evaluate SVR. A stepwise procedure was used to identify independent predictors of SVR with p=0.10 as the threshold level for variable to be entered into the final model and p=0.05 for those to be retained in the final model. All demographic and baseline clinical factors delineated in a univariate logistic regression model were candidate variable for inclusion in the multivariate model using the stepwise procedure described above.	binomial test at a 0.025 significance level. The sample size would also provide 82% power to detect a difference of 20% in SVR12 rates (50% vs. 70%) between the 12- and 16-week treatment groups. Gilead had originally calculated a historic control SVR12 rate of 18.5% for the population enrolled in FUSION. Subsequently the US Food and Drug Administration agreed that the calculation of historical SVR data as a reference was complicated in this population and recommended a simplified statistical approach using a rate of 25%.	Values for missing data were not imputed for any endpoint with the exception of HCV RNA data. Methods for handling missing data were as reported for NEUTRINO (see above). In addition, patients who were successful for SVR12 and had no further HCV RNA measurements collected were a success for SVR24 due to the high correlation between these 2 endpoints. Patients who did not have an assessment of cirrhosis performed at screening as required by the protocol were considered to be non-cirrhotic for the purposes of the sub-group analyses and for stratified statistical tests, unless an assessment of cirrhosis was made during the treatment or post-treatment period and the subject was determined to have cirrhosis.
GS-US-334-0107 POSITRON (Jacobson *et al*. 2013 a and Interim CSR)[18;72]	The study hypothesis was that SOF+RBV administered for 12 weeks would be superior to placebo in relation to the rate of SVR12.	The primary efficacy endpoint was the superiority of SOF + RBV over placebo was compared using a Cochran-Mantel-Haenszel test stratified by the presence or absence of cirrhosis using the efficacy analysis set. Superiority was demonstrated if the 2-sided Cochran-Mantel-Haenszel test p-value was <0.05 significance	It was calculated that a sample size of 180 patients in the active arm and 60 in the placebo arm would be sufficient to detect a 40% difference in sustained virologic response (SVR) between the 2 arms (using the 2-sided continuity-corrected chi-square test; α=0.05) with 99% power.	Primary analysis of the primary outcome was performed in the FAS population. Values for missing data were not imputed for any endpoint with the exception of HCV RNA data. Methods for handling missing data for HCV RNA were as reported for NEUTRINO (See above). In addition, patients who were successful for SVR12 and had no further HCV RNA

		level. *Secondary analyses of the primary outcome* Sub-group analyses of SVR12 were also performed for various pre-specified demographic and baseline clinical characteristics. In addition, pre-specified exploratory multivariate logistic-regression analyses were performed to characterise the relationship between SVR and these characteristics. A stepwise selection procedure was used to identify independent predictors of SVR, with p=0.10 as the threshold level for variables to be entered into the final model and p=0.05 for those to be retained in the final model. All demographic and baseline clinical factors delineated in a univariate logistic regression model were candidate variables for inclusion in the multivariate model using the stepwise procedure described above.		measurements collected were a success for SVR24 due to the high correlation between these 2 endpoints. Patients who did not have an assessment of cirrhosis performed at screening as required by the protocol were considered to be non-cirrhotic for the purposes of the sub-group analyses unless an assessment of cirrhosis was made during the treatment or post-treatment period and the subject was determined to have cirrhosis.
GS-US-334-0133 VALENCE (Interim CSR)[19]	The study hypothesis was that SOF+RBV administered for 12 weeks would be superior to placebo, in relation to the rate of SVR12.	The study hypothesis was planned to be tested using a XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX	It was calculated that a sample of XXX patients in the SOF+RBV group and XX in the placebo group would provide 99% power assuming SVR12 rates of XXX and XXXX, respectively in the	XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX

		XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX *Secondary analyses of the primary outcome* Secondary analyses of SVR12 were planned for treatment naïve and experienced subgroups using XXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX Exploratory analyses were also planned to assess the relationship between XXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX	two arms based on a XXXXXXXXXXXXXXXXXXXXX at a significance level of XXXX	XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXX

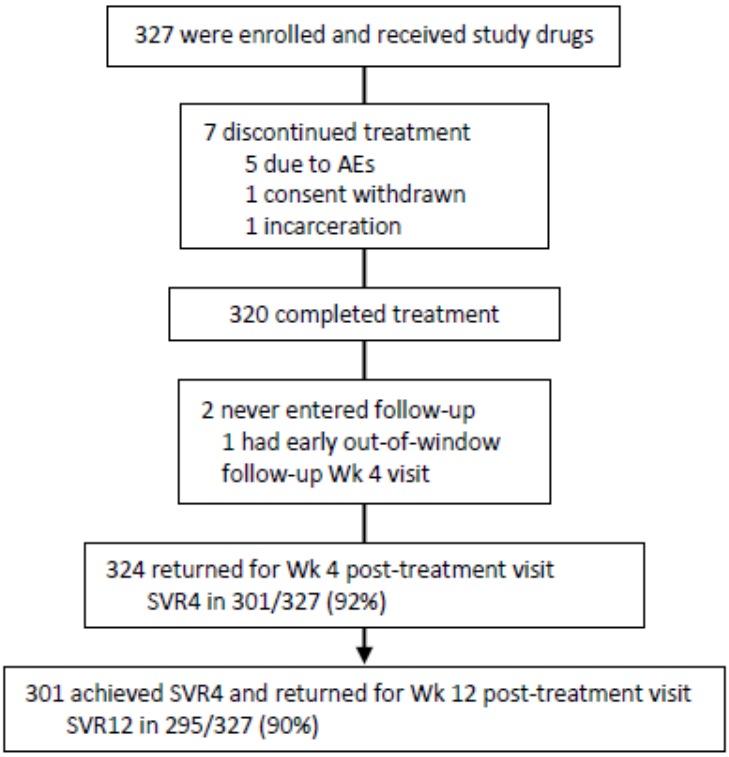
6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Planned subgroup analyses were undertaken in all studies to access the differences in SVR according to various pre-specified demographic and baseline clinical characteristics. A stepwise selection procedure was used to identify independent predictors of a SVR. Results are presented in Section 6.5.1.

Participant flow

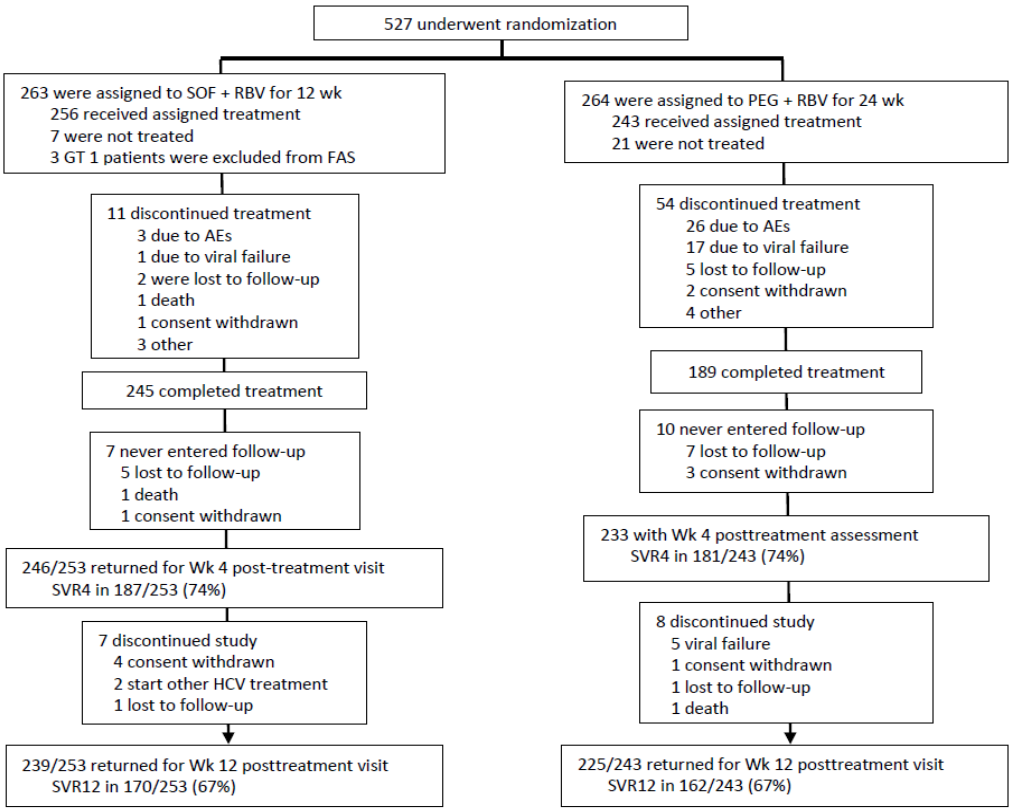
6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be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

Figure 4: NEUTRINO - Patient disposition (Lawitz et al. 2013a)[17]



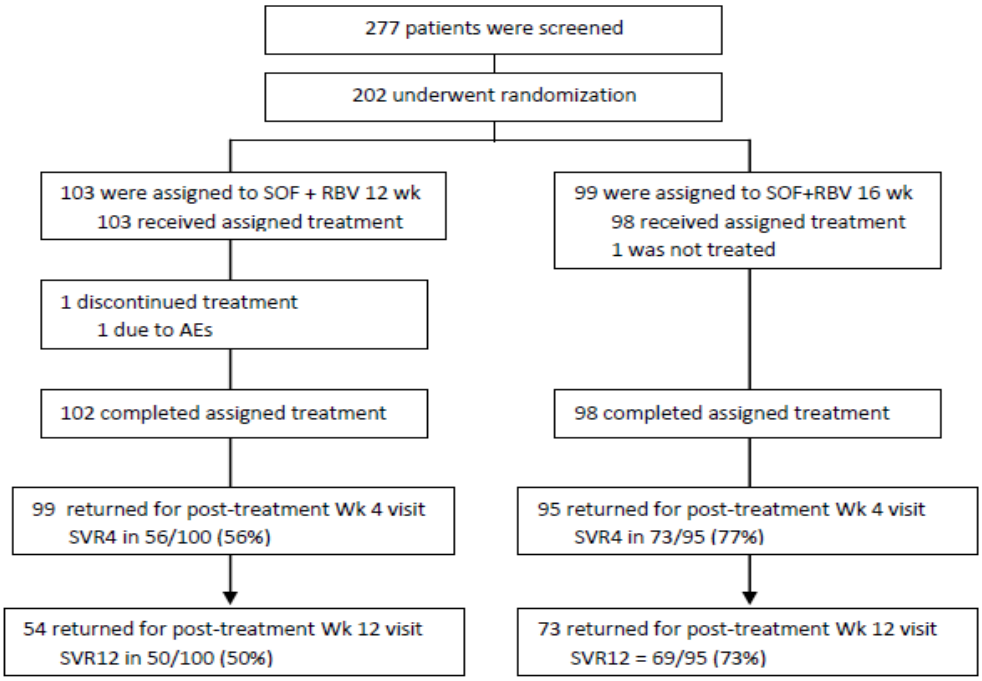
AE,Adverse event; SVR4sustained virological response at week 4 post-treatment; SVR12, sustained virological response at week 12 post-treatment, Wk, week

Figure 5: FISSION - Patient disposition (Lawitz et al. 2013a)[17]



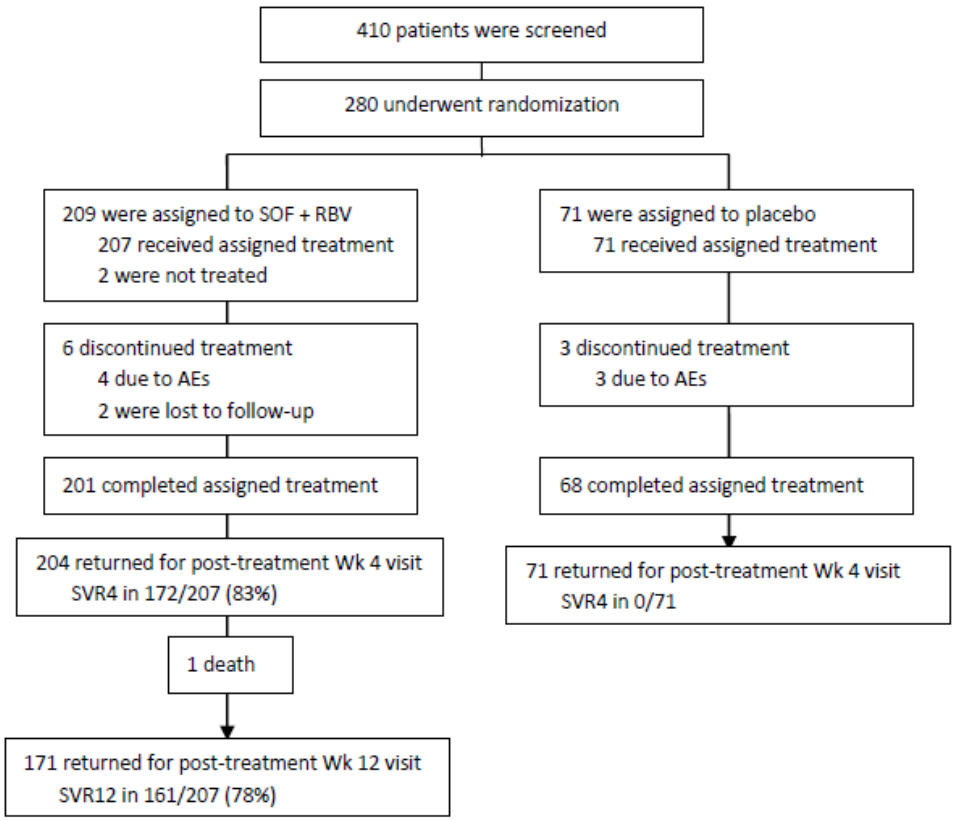
AE,Adverse events; FAS, Full analysis set; PEG, Pegylated interferon; RBV, ribavirin; SOF, sofosbuvir, SVR4, sustained virological response at week 4 post-treatment, SVR12 sustained virological response at week 12 post-treatment; wk, week

Figure 6: FUSION - Patient disposition (Jacobson et al. 2013a)[18]



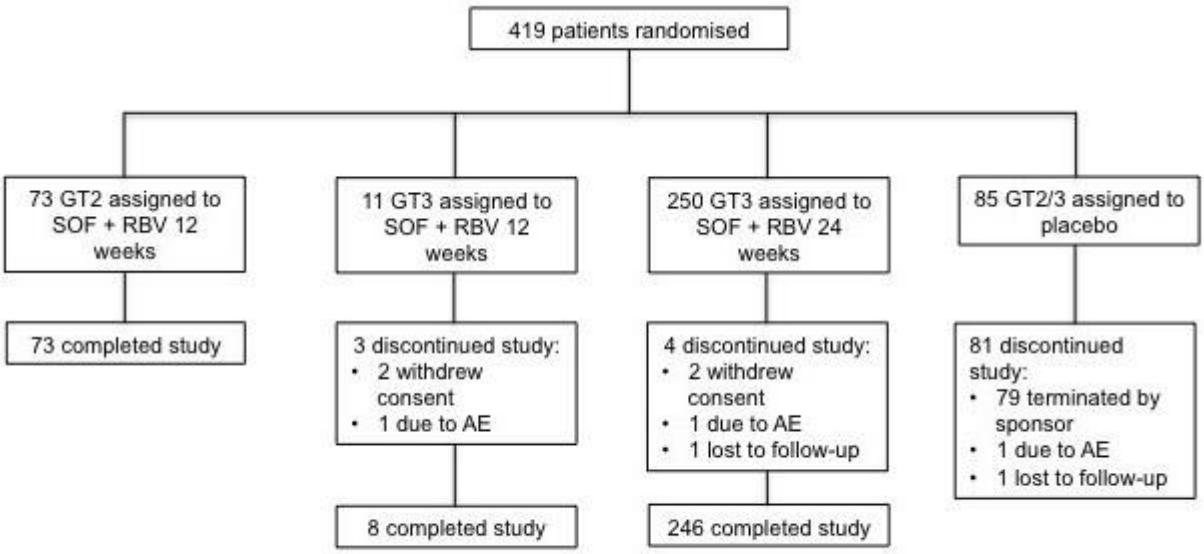
AE,adverse event, RBV, ribavirin, SOF, sofosbuvir; SVR4, sustained virological response at week 4 post-treatment, SVR12 sustained virological response at week 12 post-treatment; wk, week

Figure 7: POSITRON - Patient disposition (Jacobson et al. 2013a)[18]



AE, adverse event; RBV, ribavirin; SOF,sofosbuvir; SVR4, sustained virological response at week 4 post-treatment, SVR12 sustained virological response at week 12 post-treatment; wk, week

Figure 8: Patient disposition in VALENCE (Interim CSR)[19]



AE, adverse event; GT, genotype; RBV, ribavirin; SOF, sofosbuvir

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. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- **Was the method used to generate random allocations adequate?**
- **Was the allocation adequately concealed?**
- **Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?**
- **Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?**
- **Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?**
- **Is there any evidence to suggest that the authors measured more outcomes than they reported?**
- **Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**

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.

Detailed quality assessments of each Phase 3 trial are provided in Appendix 3, Section 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.

Table 20 Quality assessment results for RCTs

Trial no. (acronym)	GS-US-334-0110 NEUTRINO	P7977-1231 FISSION	GS-US-334-0108 FUSION	GS-US-334-0108 POSITRON	GS-US-334-0133 VALENCE
Was randomisation carried out appropriately?	N/A	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	N/A	N/A	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	N/A	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A	N/A	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	N/A	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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

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. If there is more than one RCT, tabulate the responses.**

6.5.2 **The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.**

6.5.3 **For each outcome for each included RCT, the following information should be provided**.

- **The unit of measurement.**
- **The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.**
- **A 95% confidence interval.**
- **Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.**
- **When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.**
- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**
- **Discuss and justify definitions of any clinically important differences.**
- **Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.**

6.5.3.1 HCV infected patients

6.5.3.1.1. Treatment naïve patients – NEUTRINO and FISSION

NEUTRINO –HCV GT1, 4, 5, 6 Treatment naïve

Results for the primary and secondary outcomes are provided in Table 21.

Table 21: NEUTRINO: Response during and after treatment period (Lawitz et al. 2013a)[17]

Response	SOF+PEG–IFN-2a+RBV (N=327)
HCV RNA <LLOQ†, n/N (%)	
During treatment	
At Week 2	299/327 (91)
At Week 4	321/325 (99)
At last observed measurement	326/327 (>99)
Post-treatment	
At Week 4 (SVR4)	302/327 (92)
At Week 12 (SVR12)	295/327 (90)‡
Virologic breakthrough during treatment, n (%)	0
Relapse in patients with HCV RNA <LLOQ at end of treatment†, n/N (%)	
Patients who completed treatment	25/320 (8)
Patients who did not complete treatment	3/6 (50)

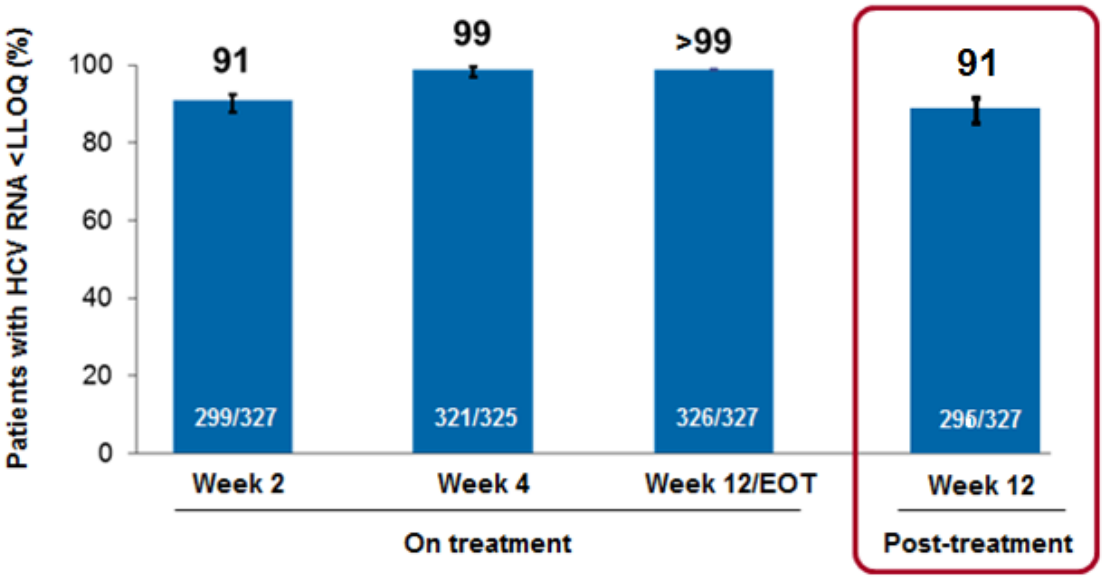
HCV, hepatitis C virus; LLOQ, lower limit of quantitation; PEG-IFN-2a, pegylated interferon alpha 2a; RBV, ribavirin, RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; SVR, sustained virological response
† Data are for patients who could be evaluated. The HCV RNA LLOQ was <25 IU/mL. ‡ A revised SVR12 rate of 91% (296/327) was calculated following the addition of one GT1 patient who was <LLOQ at SVR4, was "lost to follow-up = failure" at SVR12, but was subsequently "found" and achieved SVR24. SVR12 was back extrapolated from SVR24 for this patient.

Primary efficacy outcome - The proportion of patients with SVR12

At 12 weeks after discontinuation 90% (95% CI, 87%-93%) of patients with HCV genotype 1, 4, 5 or 6 treated with SOF + PEG-IFN-2a + RBV had an SVR. This SVR12 of 90% was superior to a 60% historical response rate adjusted for cirrhosis and expected safety benefit ($P < 0.001$) (Table 21 and Figure 9).

A revised SVR 12 rate of 91% (296/327) was subsequently calculated for licensing and is presented in the SmPC (Appendix 1.0). In this analysis one patient who was < LLOQ at SVR4 was 'lost to follow-up=failure' at SVR12 but was subsequently 'found' and achieved SVR24. As a result there was a back calculation from SVR24 to SVR 12 for this patient.

Figure 9: NEUTRINO - Percentage of patients with HCV RNA <25 IU/mL(Lawitz et al. 2013a)[17]



EOT, end of treatment; HCV, hepatitis C virus RNA; LLOQ, lower limit of quantitation; RNA, ribonucleic acid.
Red rectangle denotes primary outcome of SVR12. Values plotted are means. Error bars represent 95% CI. SVR12 rate reflects the revised analysis, incorporating one additional GT1 patient.

Subgroup analysis of SVR12

Patient responses according to baseline characteristics are shown in Figure 10.

Pre-specified sub-group analyses demonstrated that all sub-groups – age (<50 years vs. ≥50 years), sex, race, ethnicity, cirrhosis, HCV GT, HCV RNA level, BMI, ALT level, and IL28B genotype – had SVR12 rates of ≥ 80% (Figure 10).

Multivariate logistic-regression modelling to investigate covariate effects indicated that cirrhosis and a non-CC IL28B genotype were strongly associated with a reduced response.

- SVR12 rate was 92% (95% CI 89%, 95%) among patients without cirrhosis and 80% (95% CI 67%, 89%) among those with cirrhosis (p=0.0018). (Data based on original analysis; revised analysis incorporating additional GT1 patients results in SVR12 rate in non-cirrhotics of 93% [253/273])
- SVR12 rate was 98% (95% CI 93%, 100%) among patients with the IL28B CC genotype compared with 87% (95% CI 82%, 91%) among those with the non–CC IL28B genotype (p=0.006) (Based on original analysis).

Rates of SVR12 did not differ greatly by HCV genotype and were:

- GT1: 90% (262/292[b] revised analysis)
  - GT1 without cirrhosis 92% (220/240)
  - GT1 with cirrhosis: 81%
- GT4/5/6: 97% (34/35 patients)
  - GT4: 96% (27/28 patients)
  - GT5: 100% (1/1 patient)

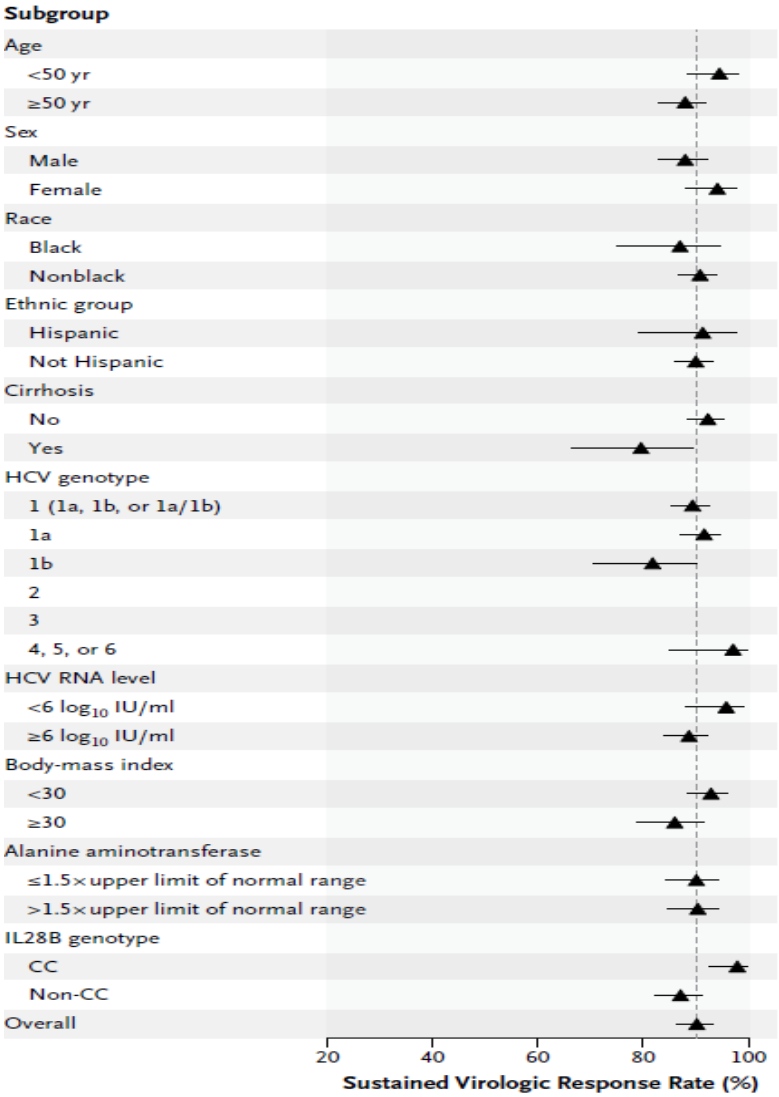
[b] Please note that the Lawitz *et al* 2013 manuscript reported a rate of 89% (261/292). The revised value added one additional GT1 patient who was <LLOQ at SVR4 and was “lost to follow-up = failure” at SVR12, but was subsequently “found” and achieved SVR24.

- GT6: 100% (6/6 patients)

Although patients with GT1a infection had a numerically higher response than patients with GT1b infection, patients with GT1b infection had slightly higher rates of several baseline characteristics typically associated with lower treatment response rates including cirrhosis, a high baseline viral load, black race and IL28B non-CC genotype, which are to have likely contributed to the observed difference.

Response rates were not affected by race or ethnicity: black (87%) versus non-black (91%) and Hispanic/Latino (91%) versus not Hispanic/Latino (90%) patients. In all of the other sub-groups, the differences in SVR12 rates were less than 10%.

Figure 10: NEUTRINO – Sub-group analyses of SVR12 (Lawitz et al. 2013a)[17]



HCV, hepatitis C virus; RNA, ribonucleic acid The position of each triangle indicates the rate of SVR 12 weeks after the end of treatment. Horizontal lines indicate 95% CIs. The vertical dotted line represents the SVR12 for the FAS.

<u>Secondary outcomes</u>

- *The proportion of patients who attain SVR4 and SVR24*

  The proportion of patients with a SVR4 weeks after the end of treatment and the proportion of patients with a SVR24 weeks after the end of treatment was 91%.

- *HCV RNA kinetics, virologic failure and viral resistance*

Potent and rapid suppression of HCV RNA was observed with a mean 4.7 log_{10} IU/mL decrease in HCV RNA after 1 week of treatment with SOF + PEG-IFN-2a + RBV, which was maintained for the duration of the study.

By week 2 and 4 of treatment, 91% (299/327) and 99% (321/325) (Figure 9) of patients had HCV RNA less than LLOQ, with 99.6% (326/327) achieving this outcome at the end of the treatment period (last observed measurement).

No patients experienced on-treatment virologic failure. Relapse after virologic response at the end of treatment occurred in 28 patients after stopping treatment, 25 of whom had completed the 12 weeks of treatment and 3 of whom did not complete the treatment course.

Deep sequencing of the HCV RNA collected at the post-treatment visits from these 28 patients showed that no previously-identified sofosbuvir or RBV-associated mutations in NS5B were present. Two NS5B substitutions were observed in >2 patients, but were not associated with change in susceptibility to sofosbuvir, IFN or RBV, *in vitro* indicating that NS5B amino acid changes observed at relapse did not reduce the viral sensitivity to these interventions.

Exploratory outcomes

- *Quality of life*

The results from the quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI) indicated that there were XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX in health-related quality of life scales between baseline and the end-of treatment responses and that XXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

The data suggest that treatment XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Table 22: NEUTRINO : Quality of life outcomes (Final CSR)[73]

Instrument	Baseline Mean (SD)	End of Treatment (Week 12) Mean (SD)	Post-treatment Week 12 Mean (SD)
SF-36, Physical component	XXXXXXXX	XXXXXXXX	XXXXXXXX
SF-36, Mental component	XXXXXXXX	XXXXXXXX	XXXXXXXX
CLDQ-HCV	XXXXXXXX	XXXXXXXX	XXXXXXXX
FACIT-F	XXXXXXXX	XXXXXXXX	XXXXXXXX
WPAI, percentage of overall work impairment	XXXXXXXX	XXXXXXXX	XXXXXXXX
WPAI, percentage of activity impairment	XXXXXXXX	XXXXXXXX	XXXXXXXX

CLDQ-HCV = Chronic Liver Disease Questionnaire - Hepatitis C; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; SD = standard deviation; SF-36 = Short Form—36 Items; WPAI = Work Productivity and Activity Impairment.

Conclusion: Study GS-US-334-0110 (NEUTRINO)

NEUTRINO included a high proportion of patients with negative predictors of response to IFN-based therapy.

99% of patients achieved an RVR and rates of SVR achieved with SOF + PEG-IFN-2a + RBV (91%) were superior to historical controls (60%) p<0.001.

High response rates were observed in all the pre-specified subgroups with SVR always ≥ 80%.

In GT1 cirrhotic 12 weeks of SOF + PEG-IFN-2a + RBV resulted in an SVR12 of 81%, the highest response reported to date in this difficult to treat patient group. High response rates (96 to 100%) response rates were achieved in GT4, 5 and 6 patients (N=35).

No patients had on-treatment virological failure.

No resistance mutations were detected in patients with virologic failure (all relapsers after the end of treatment).

FISSION – HCV GT 2, 3 Treatment naïve

Results for the primary and secondary outcomes are provided in Table 23.

Table 23: FISSION - Response during and after treatment period (Lawitz et al. 2013a)[17]

Response	SOF+RBV 12 weeks (N=253)	PEG–IFN-2a+RBV 24 weeks (N=243)
HCV RNA <LLOQ†, n/N (%)		
During treatment		
At Week 2	231/251 (92)	76/241 (32)
At Week 4	249/250 (>99)	158/236 (67)
At last observed measurement	249/253 (98)	217/243 (89)
Post-treatment		
At Week 4 (SVR4)	187/253 (74)	181/243 (74)
At Week 12 (SVR12)	170/253 (67)	162/243 (67)
Virologic breakthrough during treatment, n (%)	1 (<1)	18 (7)
Relapse in patients with HCV RNA <LLOQ at end of treatment†, n/N (%)		
Patients who completed treatment	71/242 (29)	37/188 (20)
Patients who did not complete treatment	3/7 (43)	9/29 (31)

HCV, hepatitis C virus; LLOQ, lower limit of quantitation; PEG-IFN-2a, pegylated interferon alpha 2a; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; SVR4/12, sustained virologic response at Week 4/12.

† Data are for patients who could be evaluated. The HCV RNA LLOQ was <25 IU/mL

Primary outcome - The proportion of patients with SVR12

At 12 weeks after treatment discontinuation, the SVR rate was 67% in the SOF + RBV and the PEG-IFN-2a + RBV treatment groups. SOF+RBV was non-inferior to PEG-IFN-2a + RBV with respect to the primary endpoint (absolute difference between treatment groups after adjustment for stratification 0.3%; 95% CI −7.5, 8.0; supplemental one-sided p-value associated with formal test of non-inferiority <0.001)[c].

Subgroup analyses of SVR

Rates of response in pre-specified subgroups of patients are shown in Figure 11

Of the pre-specified demographic and baseline characteristics – age (<50 years vs. ≥50 years), sex, race, ethnicity, cirrhosis, HCV GT, HCV RNA level, BMI, ALT level, and IL28B genotype – HCV GT2 (multivariate regression analysis odds ratio [OR] 42.5; 95% CI 9.5, 189.2; p<0.0001) and

[c] Note that the number of patients achieving SVR12 as presented in the published journal article (and reported herein) differs slightly from that reported in the final SmPC. This re- analysis included 3 patients who were found to have recombinant genotype 2/1 HCV infection who were excluded from the original analysis. The revised SVR12 rate is still 67% (171/256).

absence of cirrhosis (multivariate regression analysis OR 2.9; 95% CI 1.4, 189.2; p=0.005) were found to be strongly associated with high rates of SVR among patients treated with SOF + RBV.

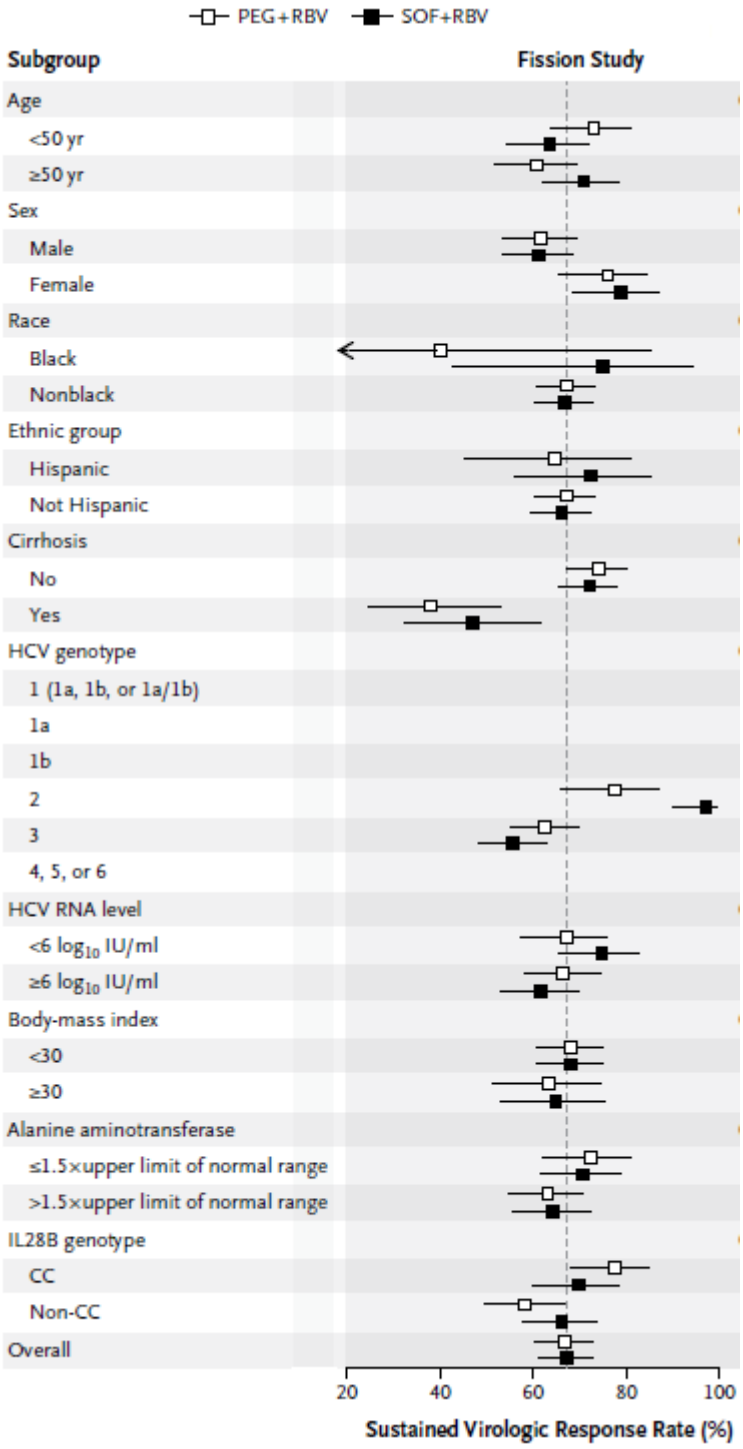
Absence/presence of cirrhosis: SVR12 was 72% (95% CI 65%, 78%) among patients without cirrhosis and 47% (95% CI 33%, 62%) among those with cirrhosis. For PEG-IFN-2a + RBV these rates were 74% (95% CI 67%, 80%) and 38% (95% CI 25%, 53%), respectively (Figure 11). Between-treatment differences were not significant in patients with or without cirrhosis.

HCV GT2: Among patients with HCV GT2 the rate of SVR12 was 97% (95% CI 90%, 100%) among patients in the SOF + RBV group and 78% (95% CI 66%, 87%) for those in the PEG-IFN-2a+RBV group (Figure 11 and Table 24). The between-treatment difference was significantly in favour of SOF + RBV (19.5%; 95% CI 8.4%, 31.5%)

HCV GT3: Among patients with HCV GT3 SVR12 rate was 56% (95% CI 48%, 63%) for SOF + RBV and 63% (95% CI 55%, 70%) for PEG-IFN-2a + RBV (Figure 11 and Table 24) with no significant between-treatment difference (−6.8%; 95% CI −17.1%, 3.5%)

SVR12 rates based on genotype and cirrhotic status are shown in Table 24, Figure 12 and Figure 13. Significant between-treatment differences in favour of sofosbuvir were maintained in the GT2 no cirrhosis group.

Figure 11: FISSION - Subgroup analyses of SVR12 (Lawitz et al. 2013a)[17]



HCV, hepatitis C virus; PEG + RBV, pegylated interferon alpha-2a and ribavirin; RNA, ribonucleic acid; SOF + RBV, sofosbuvir and ribavirin.

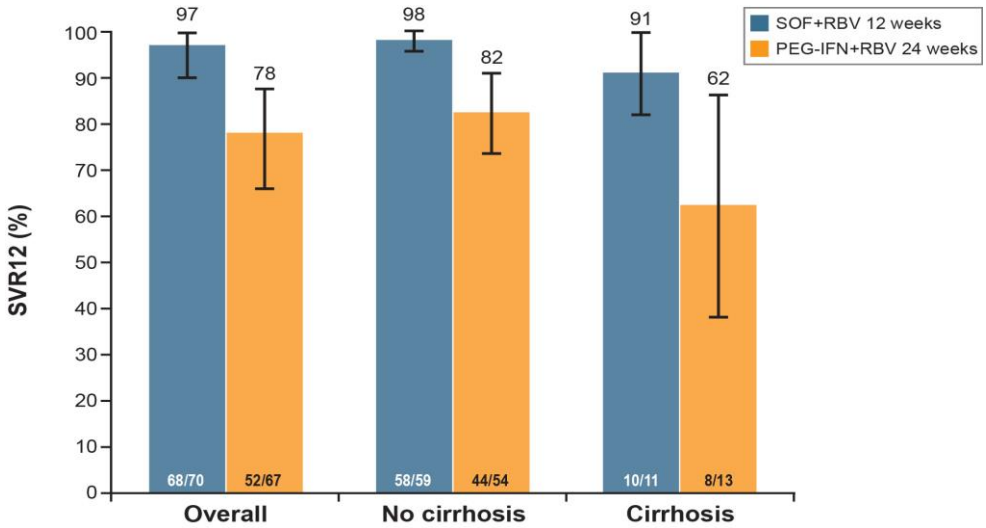
The position of each square indicates the rate of SVR 12 weeks after the end of treatment. Horizontal lines indicate 95% CIs. Arrows indicate CIs that exceed the x-axis scale. The vertical dotted line represents the SVR12 for the full analysis set.

Table 24 : FISSION – SVR Rate by genotype and presence of cirrhosis (Lawitz et al. 2013a and final CSR)[17;74]

Response,n/N, %	SOF+RBV 12 weeks (N=253)	PEG-IFN-2a+RBV 24 weeks (N=243)	SOF+RBV vs. PEG-IFN-2a+RBV Proportional difference (95% CI)
GT2 overall	68/70 97.%	52/67 77.6 (65.8, 89.6)	19.5 (8.4, 31.5)
No cirrhosis	XXXXX XXXXX	XXXXX XXXXX	XXXXXXXXXX
Cirrhosis	XXXXX XXXXX	XXXXX XXXXX	XXXXXXXXXX
GT3 Overall	102/183 55.7%	110/176 62.5%	−6.8 (−17.1, 3.5)
No cirrhosis	89/145 61.4 %	99/139 71.2 %	−9.8 XXXXXXXXX
Cirrhosis	13/38 34.2 %	11/37 29.7%	4.5 XXXXXXXXX

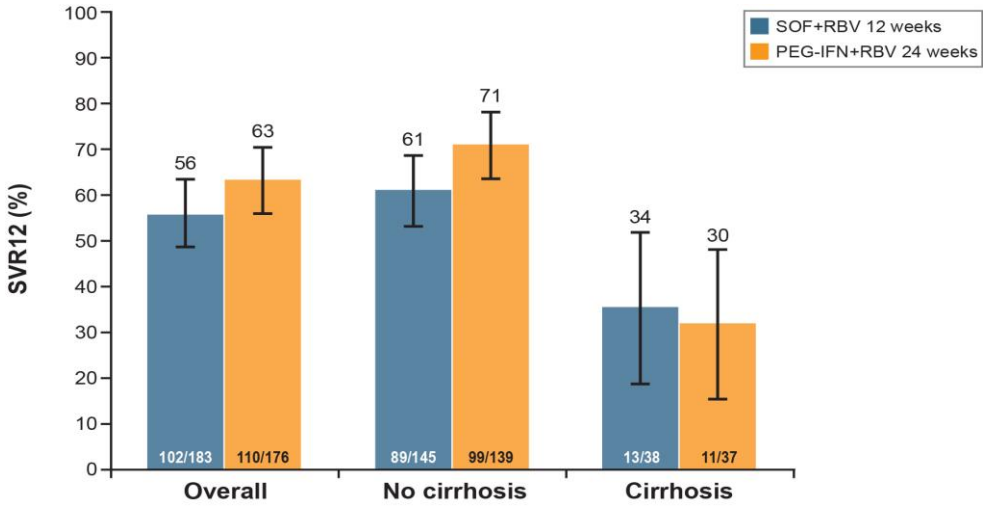
GT, genotype; PEG-IFN-2a pegylated interferon alpha 2a; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at Week 12.

Figure 12: FISSION - Percentage of patients with HCV GT2 with SVR12 by cirrhosis status



PEG-IFN+RBV, pegylated interferon alpha 2a and ribavirin; SOF+RBV, sofosbuvir and ribavirin; SVR12, sustained virologic response at Week 12.
Values plotted are means. Error bars represent 95% CI.

Figure 13:FISSION - Percentage of patients with GT3 with SVR12 by cirrhosis status



PEG-IFN+RBV, pegylated interferon alpha 2a and ribavirin; SOF+RBV, sofosbuvir and ribavirin; SVR12, sustained virologic response at Week 12.
Values plotted are means. Error bars represent 95% CI.

<u>Secondary outcomes</u>

- *The proportion of patients who attain SVR4 and SVR24*

  The proportion of patients with a SVR 4 weeks after the end of treatment was similar between the treatment groups (Both 74%; Table 23). The proportion of patients with an SVR 24 of 67% in the SOF + RBV compared with 65% in the PEG-IFN-2a + RBV group

- *HCV RNA kinetics, virologic failure and viral resistance*

  Suppression of HCV RNA was more rapid with SOF + RBV compared with PEG-IFN-2a + RBV. By Week 2, 92.0% of patients in the SOF + RBV group (231/251) and 32% of patients in the PEG-IFN-2a + RBV group (76/241) had achieved HCV RNA <LLOQ, representing a between-group difference in the proportions of 60.6% (95% CI 53.8%, 67.3%) in favour of SOF + RBV. The differences between groups were less apparent over time, but SOF + RBV was numerically higher at all the time points through Week 12 versus PEG-IFN-2a + RBV. By Week 4, SVR rate was >99% versus 67%, and at the last observed measurement it was 98% compared with 89% (Table 21).

  Only one SOF + RBV patient (<1%) had viral breakthrough during Week 8 of treatment. Plasma levels of sofosbuvir in this patient were undetectable at that time, suggesting non-adherence to treatment. By comparison, virologic breakthrough occurred in 18 patients (7%) in the PEG-IFN-2a + RBV group while on treatment (Table 21).

  Relapse occurred in 29% (n=71) of the 242 patients who completed treatment with SOF + RBV and in 43% (n=3) of the 7 patients who did not complete this treatment. In the PEG-IFN-2a + RBV group, 20% (n=37) of the 188 patients who completed treatment relapsed as did 31% (n=9) of the 29 patients who did not complete PEG-IFN-2a + RBV treatment. There was a high concordance (>99%) between SVR rates at 12 and 24 weeks post-treatment among patients who received SOF+RBV; only 1 of 166 patients who could be evaluated had a virologic relapse after post-treatment Week 12.

  Deep sequencing of the HCV RNA collected at the post-treatment visits from the 74 patients who relapsed after discontinuation of SOF + RBV showed that no known sofosbuvir - resistance mutations in NS5B (e.g. S282T) was present. No reduction in susceptibility to

sofosbuvir or RBV was observed among patient samples containing NS5B substitutions, indicating that NS5B amino acid changes observed at relapse did not reduce the viral sensitivity to sofosbuvir or RBV.

<u>Exploratory outcomes</u>

Quality of life was determined using SF-36. For the composite Physical Component score, patients in the SOF + RBV group XXXXXX and the PEG-IFN-2a + RBV group XXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXX[74].

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XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXX[74].

Conclusion – FISSION

In FISSION, a non-inferiority, open-label, randomised study, HCV treatment-naïve patients with GT2 and GT3 HCV infection had a rate of sustained virologic response of 67% 12 weeks after the end of treatment with SOF + RBV (12 weeks treatment), which was non-inferior to PEG + RBV (24 weeks treatment) meeting the primary endpoint of non-inferiority versus standard of care (PEG + RBV).

Patients treated with SOF + RBV demonstrated a rapid decline in HCV RBA with >99% of patients achieving an RVR outcome (HCV RNA<LLOQ) at week 4 compared with 67% of patients treated with PEG+RBV.

In patients with HCV GT 2 treatment with SOF + RBV for 12 weeks achieved a very high rate of SVR12 (97% vs. 78% with PEG-IFN-2a + RBV). In GT 3 patients, treatment with SOF+RBV for 12 weeks resulted in similar overall SVR12 rates to PEG + RBV (56% and 63%, respectively).

Significant between-treatment differences in favour of SOF + RBV versus PEG-IFN-2a + RBV were observed in GT2 patients overall and in GT2 patients without cirrhosis. SVR12 in GT2 was high irrespective of cirrhosis (98% in patients without cirrhosis vs. 91% in patients with cirrhosis; compared with 82% and 62% respectively with PEG-IFN-2a + RBV). SVR 12 in GT3 with patients

with cirrhosis was similar between the treatment groups (34% SOF + RBV vs. 30% PEG-IFN-2a + RBV)

No resistance mutations were detected in SOF + RBV patients who relapsed.

The data from this study are consistent with the growing expert opinion that GT 2 and GT 3 HCV behave differently and should be considered as separate populations. Studies evaluating longer durations of SOF + RBV treatment to further increase response rates in GT 3 patients include FUSION and VALENCE and are reported below.

6.5.3.1.2 HCV GT 2 or 3 Treatment Experienced Patients -FUSION

Results for the primary and secondary outcomes are provided in Table 25.

Table 25: FUSION Response during and after treatment period (Jacobson et al. 2013a)[18]

Response	SOF+RBV 12 weeks (N=100)	SOF+RBV 16 weeks (N=95)
HCV RNA <LLOQ†, n/N (%)		
During treatment		
At Week 2	81/100 (81)	83/95 (87)
At Week 4	97/100 (97)	93/95 (98)
At Week 12	100/100 (100)	95/95 (100)
At Week 16	-	95/95 (100)
Post-treatment		
At Week 4 (SVR4)	56/100 (56)	73/95 (77)
At Week 12 (SVR12)	50/100 (50)	69/95 (73)
Virologic breakthrough during treatment, n (%)	0	0
Relapse in patients with HCV RNA <LLOQ at end of treatment†, n/N (%)		
Patients who completed treatment	46/99 (46)	26/95 (27)
Patients who did not complete treatment	1/1 (100)	0

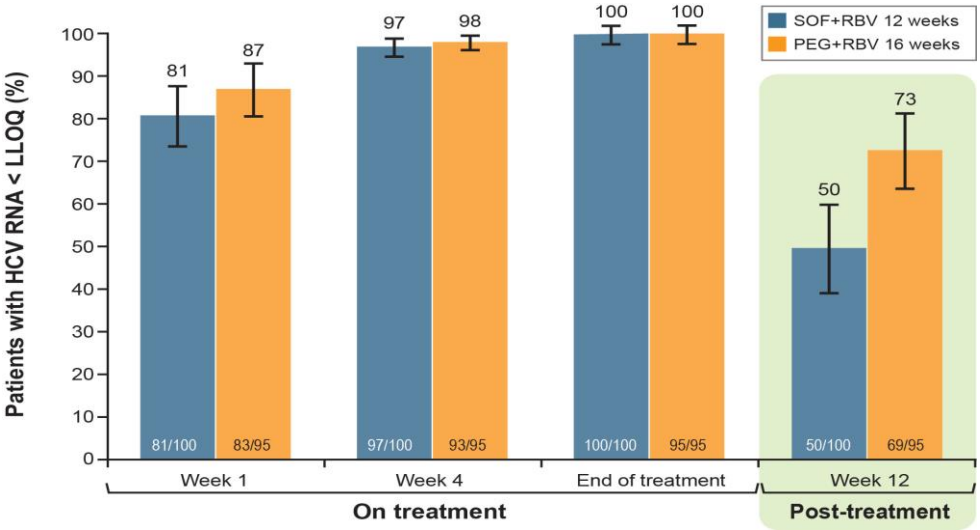
HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR4/12, sustained virologic response at Week 4/12.

† Data are for patients for whom HCV RNA data were available. The HCV RNA LLOQ was <25 IU/mL.

Primary endpoint – The proportion of patients with SVR12

In this population of patients with HCV GT2 or GT3 for whom prior treatment had failed, rates of SVR achieved 12 weeks after treatment discontinuation with SOF+RBV were superior to the historical control rate of 25%, with rates of 50% (95% CI, 40 to 60) in the 12-week group and 73% (95% CI, 63 to 81) in the 16-week group (P<0.001 for each comparison)[d] (Figure 14) (Table 25).

Figure 14: FUSION - Percentage of patients with HCV RNA < 25 IU/mL (Jacobson *et al.* 2013a)[18]



Secondary analysis: SVR12 for the 12-week versus 16-week treatment groups

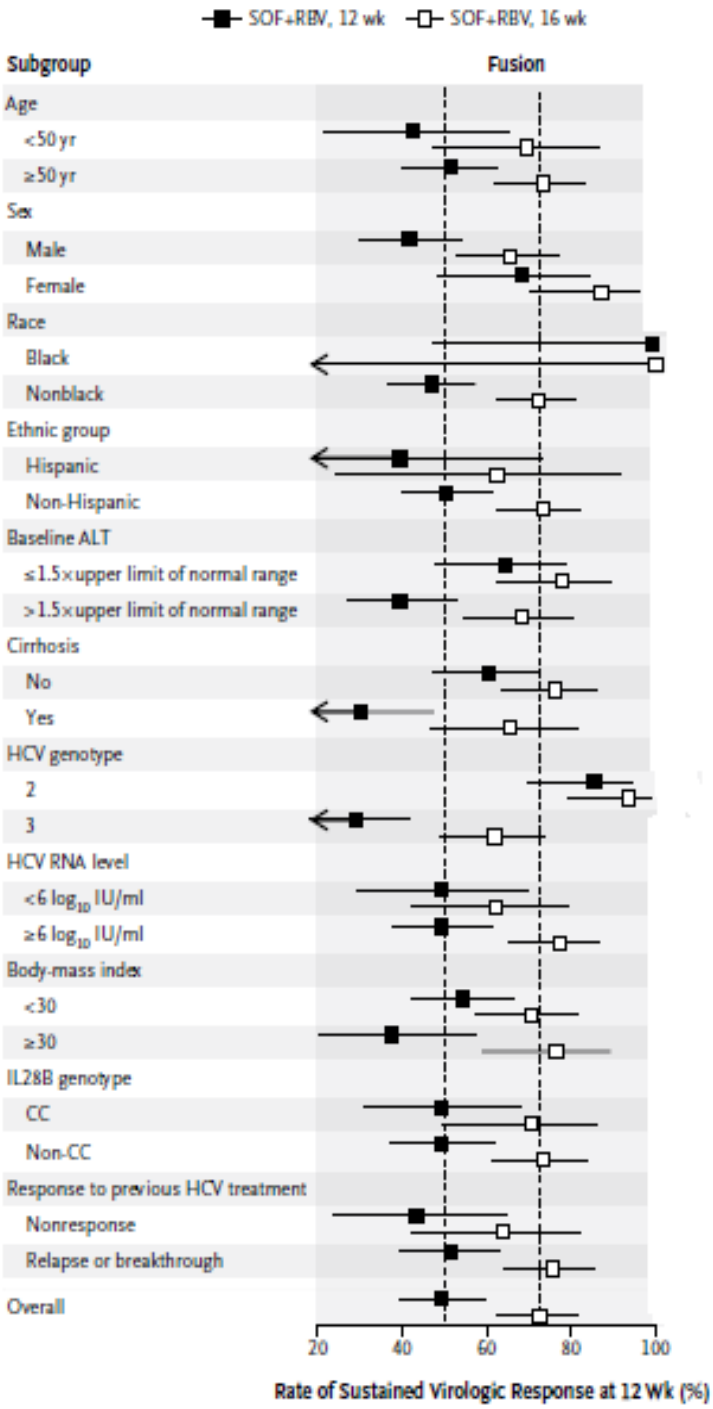
The proportion of patients with a SVR12 was significantly higher for the group receiving 16 weeks of SOF + RBV than for the group treated for 12 weeks (difference −23%; 95% CI −35, −11; p<0.001).

Subgroup analysis

The rates of SVR in various patient subgroups are shown in Figure 15.

[d] Note that the number of patients achieving SVR12 as presented in the published journal article (and reported herein) differs slightly from that reported in the final SmPC. This re-analysis included 6 patients who were found to have recombinant GT2/1 HCV infection who were excluded from the original analysis. The revised SVR12 rates are 50% (51/103) and 71% (70/98) for the 12-week and 16-week groups, respectively.

Figure 15: FUSION – Sub-group analyses of SVR12 (Jacobson *et al.* 2013a)[18]



HCV, hepatitis C virus; RNA, ribonucleic acid; SOF + RBV, sofosbuvir and ribavirin.

The position of each square indicates the rate of SVR 12 weeks after the end of treatment. Horizontal lines indicate 95% CIs. Arrows indicate CIs that exceed the x-axis scale. The vertical dotted line represents the SVR12 for the full analysis set.

Multivariate logistic-regression modelling, performed independently for each treatment group to determine covariate effects, identified HCV genotype and liver cirrhosis as significant factors associated with differences in SVR12 rate.

- HCV genotype

  HCV GT2 infection was significantly associated with a higher rate of SVR12 in both the 12- and 16-week treatment groups, compared with GT3 infection (12-week: OR 21.5; 95% CI 6.1, 75.1; p<0.0001; 16-week: OR 10.5; 95% CI 2.3, 49.2; p=0.0028). A significantly lower rate of SVR12 in the 12-week treatment group indicates that the longer treatment period of 16 weeks reduces the rate of relapse for patients with GT3 infection:

  - GT2: SVR12 rates in the 12-week and 16-week treatment groups were 86% (31/36) and 94% (30/32), respectively (difference −8%; 95% CI −24, 9)

  - GT3: SVR12 rates in the 12-week and 16-week treatment groups were 30% (19/64) and 62% (39/63), respectively (difference −32%; 95% CI −48, −15).

- Cirrhosis

  The absence of cirrhosis was associated with a higher rate of SVR12 among patients who received 12 weeks of treatment (OR 3.1; 95% CI 1.0, 9.5; p=0.046), particularly among those with HCV GT3 infection. A significant difference was observed between the 12-week and 16-week treatment groups with respect to GT3 infection irrespective of the presence of cirrhosis, suggesting that patients with GT3 infection would achieve additional benefit from the longer 16-week treatment duration with sofosbuvir (Table 26).

Table 26: FUSION SVR12 rate by genotype and presence of cirrhosis (Jacobson et al. 2013a)[18]

Response n/N ,%	SOF+RBV 12 weeks (N=100)	SOF+RBV 16 weeks (N=95)	SOF+RBV 12 weeks vs. SOF+RBV 16 weeks, Proportional difference (95% CI)
GT2, no cirrhosis	25/26 96%	22/23 100%	−3.8% (−20.2%, 11.3%)
GT2 and cirrhosis	6/10 60%	7/9 78%	−17.8% (−58.0%, 26.8%)
GT3, no cirrhosis	15/38 37%	63% 25/40	−25.7% (−46.5%, −2.9%)
GT3 and cirrhosis	5/26 19%	14/23 61%	−41.6% (−65.0%, −11.8%)

GT, genotype; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at Week 12.

<u>*Secondary outcomes*</u>

- *The proportion of patients who attained SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)*

  A total of 56% of patients (56 of 100) in the SOF + RBV 12-week group and 77% of patients (73 of 95) in the SOF + RBV 16-week group achieved SVR4. The proportion of patients with SVR 24 weeks after the end of treatment (SVR24) was 50% in the 12 week group and 72% in the 16-week group.

- *HCV RNA kinetics, virologic failure and viral resistance*

  Response to treatment was rapid for the 12-week and 16-week treatment groups 81% and 87% of patients respectively had HCV RNA below the LLOQ at Week 2 of treatment, and this increased to 97% and 98% at week 4. By week 12 all patients had achieved a response to treatment.

  Mean (standard deviation [SD]) HCV RNA levels ($\log_{10}$ IU/mL) at Week 1 were XXXXXXXXX XXXXXXXXXXXXXXXX 12-week and 16-week groups, respectively, equating to a change XXXXXX maintained throughout the treatment period.

None of the patients in either treatment group experienced virologic breakthrough during treatment . Relapse after an end-of-treatment SVR occurred in 47 patients in the 12-week group and 26 patients in the 16-week group. All but 1 of these patients completed treatment. Most relapses occurred XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Sequencing of the HCV RNA collected at the post-treatment visits from the patients who relapsed after discontinuation of SOF + RBV showed that no known sofosbuvir-resistance mutations in NS5B (e.g.S282T) were present. No reduction in susceptibility to SOF or RBV was observed among patient samples containing NS5B substitutions, indicating that NS5B amino acid changes observed at relapse did not reduce the viral sensitivity to SOFor RBV.

<u>Exploratory outcomes</u>

- *Quality of life*

The overall CLDQ-HCV score_did not decrease significantly in the 16-week SOF+RBV group or the 12-week SOF + RBV group. There were no significant differences in overall scores between the groups Table 27.

For FACIT-F, WPAI, and SF-36, quality of life scores XXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXX

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Table 27: FUSION: Quality of life outcomes (Final CSR)[75]

	SOF+RBV 12 weeks			SOF+RBV 16 weeks		
Instrument	**Baseline Mean (SD)**	**End of Treatment (Week 12) Mean (SD)**	**Post-treatment Week 12 Mean (SD)**	**Baseline Mean (SD)**	**End of Treatment (Week 12) Mean (SD)**	**Post-treatment Week 12 Mean (SD)**
SF-36, Physical component	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
SF-36, Mental component	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
CLDQ-HCV	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
FACIT-F Total score	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
WPAI, percentage of overall work impairment	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
WPAI, percentage of activity impairment	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

CLDQ-HCV, Chronic Liver Disease Questionnaire - Hepatitis C; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; SD, standard deviation; SF-36, Short Form—36 Items; WPAI, Work Productivity and Activity Impairment.

Conclusion - FUSION

In FUSION, a double-blind, randomised study, HCV patients with GT2/3 HCV infection who had failed on prior IFN treatment achieved SVR12 (a difficult to treat population who currently have limited treatment options) rates of 50% and 73%, with 12 weeks and 16 weeks of SOF + RBV treatment, respectively. Response to treatment was rapid (within 2 weeks) and all patients had unquantifiable HCV RNA levels by the end of treatment and met the primary endpoint of superiority over the historical control ($p<0.001$ for each comparison).

Genotype was an important factor in determining SVR12 and the effect of extended treatment duration. In GT2 patients treated for 16 weeks resulted in a similar SVR12 rate to that achieved after 12 weeks of treatment (84% vs. 86% respectively). In GT3 patients the SVR12 rate was significantly higher after 16 weeks treatment and more than double that achieved following 12 weeks treatment (62% vs. 30% respectively).

In GT3 patients, compared with 12 weeks of treatment, 16 weeks of treatment with SOF + RBV improved SVR12 more than 3-fold (19% vs. 61%, respectively) in cirrhotic patients and almost 2-fold (37% vs. 63%, respectively) in patients without cirrhosis.

No resistance mutations were detected in SOF + RBV patients who relapsed.

NOTE: Following the results of the FUSION study it was postulated that an even longer duration of treatment may offer GT3 patients an improved chance of achieving SVR. This is being investigated in the European Phase 3 VALENCE study reported below in which treatment duration in patients with GT3 infection is extended to 24 weeks.

6.5.3.1.4 HCV GT2,3 treatment naïve and experienced patients – POSITRON

Results for the primary and secondary outcomes are provided in Table 28.

Table 28 : POSITRON: Response during and after treatment period (Jacobson et al. 2013a)[18]

Response	SOF+RBV 12 weeks (N=207)	Placebo 12 weeks (N=71)
HCV RNA <LLOQ†, n/N (%)		
During treatment		
At Week 2	186/205 (91)	0/70
At Week 4	202/204 (99)	0/70
At Week 12	202/202 (100)	0/71
Post-treatment		
At Week 4 (SVR4)	172/207 (83)	0/68
At Week 12 (SVR12)	161/207 (78)	0/68
Virologic breakthrough during treatment, n (%)	0	-
Relapse in patients with HCV RNA <LLOQ at end of treatment†, n/N (%)		
Patients who completed treatment	40/201 (20)	-
Patients who did not complete treatment	2/4 (50)	-

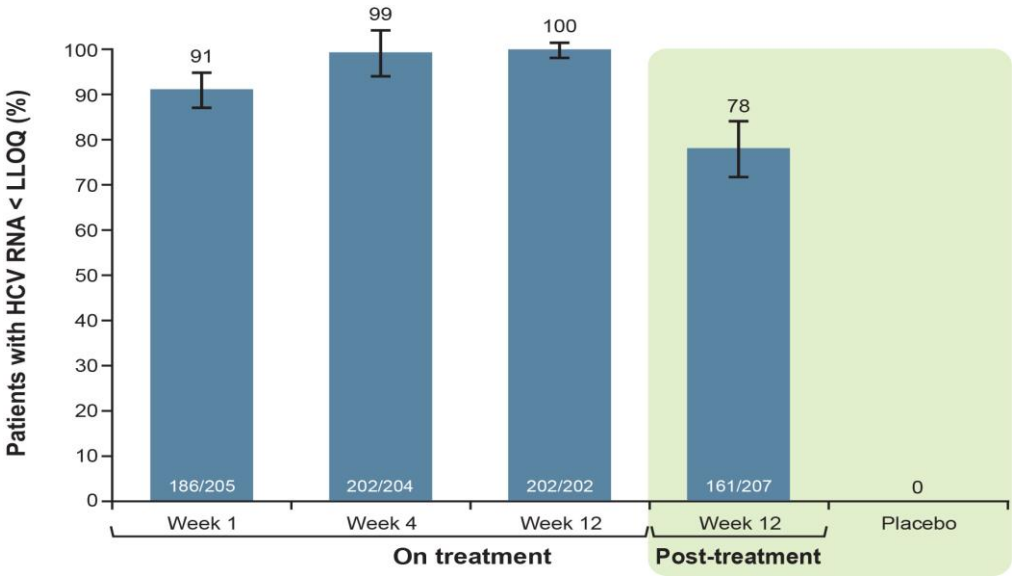
HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR4/12, sustained virologic response at Week 4/12.

† Data are for patients for whom HCV RNA data were available. The HCV RNA LLOQ was <25 IU/mL.

Primary outcome– The proportion of patients with SVR12

In this population of patients who were unsuitable for IFN (e.g. patients who were ineligible for, intolerant of or unwilling to take IFN based treatment) SOF+RBV was superior to placebo; SVR 12 was achieved by 78% of patients (95% confidence interval [CI], 72 to 83) receiving SOF + RBV and 0% in the placebo group (P<0.001) (Table 28 and Figure 16).

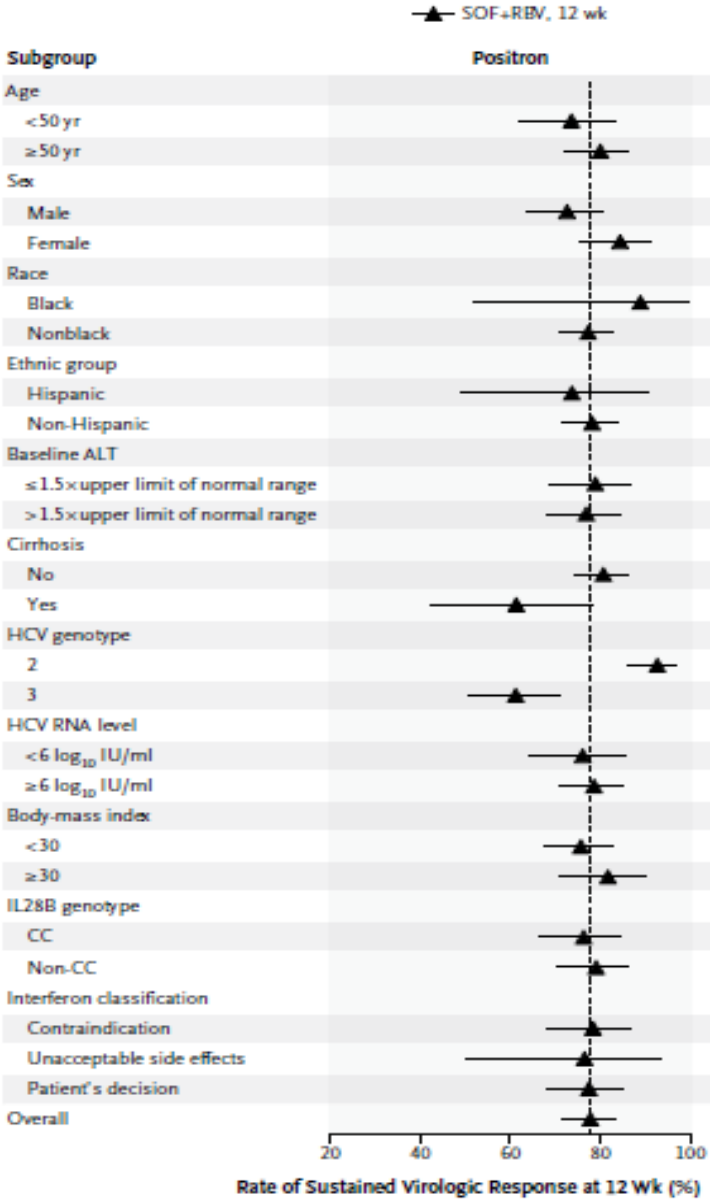
Figure 16: POSITRON: Percentage of patients with HCV RNA < 25 IU/mL (Jacobson et al. 2013a)[18]



Subgroup analysis

Rates of SVR in patient subgroups are shown in Figure 17.

Figure 17: Rates of SVR according to demographics and baseline clinical characteristics in POSITRON (Jacobson et al. 2013a)[18]



HCV, hepatitis C virus; RNA, ribonucleic acid; SOF + RBV, sofosbuvir and ribavirin.

The position of each triangle indicates the rate of SVR 12 weeks after the end of treatment. Horizontal lines indicate 95% CIs. The vertical dotted line represents the SVR12 for the full analysis set.

Multivariate logistic-regression modelling demonstrated that HCV GT2 was significantly associated with a higher rate of SVR12, compared with GT3 infection (OR 8.7; 95% CI 3.6, 20.7; p<0.0001). In these patients who were unsuitable for IFN the specific reason – ineligibility, intolerance or unwillingness – was not a predictor of SVR.

Among patients treated with SOF + RBV, SVR12 rates were 93% with HCV GT2 infection and 61% with HCV GT3 infection (Table 29).

Presence of cirrhosis did not affect the rate of SVR12 in GT2 patients (94% vs. 92% for no cirrhosis). However, SVR12 rate was higher in those HCV GT3 patients without cirrhosis (68%) compared with those with cirrhosis (21%).

Table 29: POSITRON: SVR12 rate by genotype and presence of cirrhosis(Jacobson et al. 2013a)[18]

Classification	GT2 (N=109)	GT3 (N=98)
SVR12, n/N (%)		
All	101/109 (93)	60/98 (61)
No cirrhosis	85/92 (92)	57/84 (68)
Cirrhosis	16/17 (94)	3/14 (21)

GT, genotype; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at Week 12.

Secondary Outcomes

- *The proportion of patients who attain SVR4 and SVR24*

  A total of 83% of patients in the SOF + RBV group and 0% of patients in the placebo group achieved SVR4. The SVR24 rate was 78%; there was complete concordance (100%) between rates of SVR12 and SVR24 among patients who received SOF + RBV, with none of the 153 patients who could be evaluated having a relapse after Week 12.

- *HCV RNA kinetics, virologic failure and viral resistance*

  Response to treatment was rapid in the SOF + RBV group. 91% had HCV RNA below the LLOQ at Week 2 of treatment, and this increased to 99% at week 4. By week 12 all patients had achieved a response to treatment.

  Mean (SD) HCV RNA level ($\log_{10}$ IU/mL) at Week 1 was 1.85 (0.531) in the SOF+RBV group, equating to a change from baseline of −4.43 (0.650). This reduction was maintained throughout the treatment period.

  None of the SOF-treated patients experienced virologic breakthrough during treatment. Forty two (42) patients relapsed after achieving an end-of-treatment SVR; 40 who completed treatment and two who did not. Sequencing of the HCV RNA collected at the post-treatment visits from the patients who relapsed after discontinuation of SOF + RBV showed that no known SOF- or RBV-associated resistance mutations in NS5B were present. No reduction in susceptibility to SOF or RBV was observed among patient samples containing NS5B substitutions, indicating that NS5B amino acid changes observed at relapse did not reduce the viral sensitivity to SOF or RBV.

<u>Exploratory Outcomes:</u>

- Effect of treatment on health-related quality of life

  During the treatment period (baseline through Week 12), there were decreases (worsening) in the eight SF-36 scales and the Mental Component and Physical Component scores in both treatment groups. In the SOF + RBV group there were statistically significant ($p<0.001$) differences from baseline in the Physical Function scale, Role Physical, Vitality, Social Functioning, Role Emotional, and Mental Health scales; however, there were no significant differences from placebo at any time point (Final CSR)[76].

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Conclusion - POSITRON

In POSITRON, a double-blind, randomised, placebo-controlled study of HCV patients with GT2 or GT3 HCV infection for whom IFN-based treatment was unsuitable, SVR12 was achieved by 78% of patients in the SOF+RBV group compared with 0% patients in the placebo group ($p<0.001$) and the primary endpoint of superiority over placebo was met.

POSITRON included patients:

- for whom IFN-based treatment was not an option and who currently have no treatment options
- a high proportion of patients with negative predictors of response to IFN

Despite this all patients (100%) achieved an RVR (HCV RNA levels below the LLOQ) at by the end of treatment.

Efficacy was significantly increased among patients with HCV GT2 infection compared with GT3. In patients with GT2 SVR 12 was 94% in patients with cirrhosis and 92% in patients without cirrhosis. Presence of cirrhosis appeared to reduce the SVR12 response in GT3 patients. In total 91% and 61% of GT3 patients achieved SVR 12. SVR12 was 21% in patients with cirrhosis and 68% in patients without cirrhosis.

No resistance mutations were detected in SOF + RBV patients who relapsed.

In POSITRON patients in whom IFN-based treatment was not an option treated with SOF + RBV achieved SVR rates similar to those seen in the FISSION study for treatment-naïve patients.

6.5.3.1.5 HCV GT2, 3 treatment naïve and treatment experienced -VALENCE

Results for the primary and secondary outcomes are provided in Table 30. The results provided are derived from an interim analysis and therefore some outcomes have yet to be reported. Data for SVR12 are available for all patients with GT2 and GT3 HCV infection who received 12 weeks of SOF + RBV treatment. Post-treatment follow-up is still ongoing for a small number of patients with GT3 HCV infection who received 24 weeks of SOF + RBV treatment. Available SVR12 data are presented in this submission with missing values imputed as failures.

Table 30: VALENCE - Response during and after treatment events (CSR)[19]

Response	GT2 SOF+RBV 12 weeks (N=73)	GT3 SOF+RBV 12 weeks (N=11)	GT3 SOF+RBV 24 weeks (N=250)
Last observed on-treatment HCV RNA <LLOQ†, n	XX	XX	XXX
Post-treatment, n/N (%)			
At Week 4 (SVR4)	XXXXXXX	XXXXXX	XXXXXX
At Week 12 (SVR12)	XXXXXXX	XXXXXX	XXXXXX
Overall virologic failure, n (%)	XXXXXXX	XXXXXX	XXXXXX
Relapse, n/N (%)	XXXXXX	XXXXXX	XXXXXX
Patients who completed treatment, n (%)	XXXXXX	XXXXXX	XXXXXX
Patients who did not complete treatment, n (%)	XXX	XXXXXX	XXXXXX
On-treatment virologic failure, n (%)	XXX	XXX	XXX

HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR4/12, sustained virologic response at Week 4/12. †HCV RNA LLOQ was <25 IU/mL.

Primary outcome– The proportion of patients with SVR12

In GT2 patients treated with SOF + RBV for 12 weeks, the SVR12 rate was 93% (68/73), consistent with other studies.

SOF + RBV given for 24 weeks resulted in SVR12 XXXXX[5] XXXXXX of GT3 HCV-infected patientsTable 30

Exploratory analysis: Identification of demographic and baseline clinical characteristics influencing SVR12

In all subgroups of GT2 HCV-infected patients treated with SOF + RBV for 12 weeks, high rates of SVR12 were achieved (≥ 88%), irrespective of prior treatment experience and presence/absence of cirrhosis (Table 31).

In treatment-naive GT3 patients, SOF + RBV given for 24 weeks resulted in SVR12 rates >90%, irrespective of cirrhosis status.

[5] Value as reported in CSR. Poster reports 85% (212/250)

In treatment-experienced GT3 patients, SOF + RBV given for 24 weeks resulted in SVR12 rates of 60% and 85% in those with or without cirrhosis.

Table 31: VALENCE - SVR12 by subgroup (CSR)[19]

SVR12 response	GT2 SOF+RBV 12 weeks (N=73)	GT3 SOF+RBV 12 weeks (N=11)	GT3 SOF+RBV 24 weeks (N=250)
Treatment-naïve, n/N (%)	XXXXXXX	XXXXXX	98/105 (93)
Non-cirrhotic	29/30 (97)	XXX	86/92 (94)
Cirrhotic	2/2 (100)	XXX	12/13 (92)
Treatment-experienced, n/N (%)	37/41 (90)	XXXXX	112/145 (77)
Non-cirrhotic	30/33 (91)	XXXXX	85/100 (85)
Cirrhotic	7/8 (88)	XXX	27/45 (60)
Treatment experience classification, n/N (%)			
IFN intolerant	XXXXXXX	XXX	XXXXXXX
Non-response	XXXXXXX	XXXXX	XXXXXXX
Relapse/breakthrough	XXXXXXX	XXXXX	XXXXXXX

GT, genotype; HCV, hepatitis C virus; IFN, interferon; ; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at Week 12.

<u>Secondary efficacy outcomes</u>

- The proportion of patients who attain SVR4 and SVR24

  In patients treated with SOF + RBV for 12 weeks, SVR4 was achieved in XXXXX XXX of those with XXXXXXXXXXXX. A total of XXXXXXXXXXXXXXXXXXX XXXX patients who received SOF + RBV for 24 weeks achieved SVR4 (Table 30). SVR24 data has yet to be reported.

- *HCV RNA kinetics and viral resistance*

  Response to treatment was rapid in the SOF + RBV groups, with HCV RNA reaching the LLOQ by Week 4 of treatment (Figure 18).

  No GT2 HCV-infected patients treated with SOF + RBV for 12 weeks had on-treatment virologic failure. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

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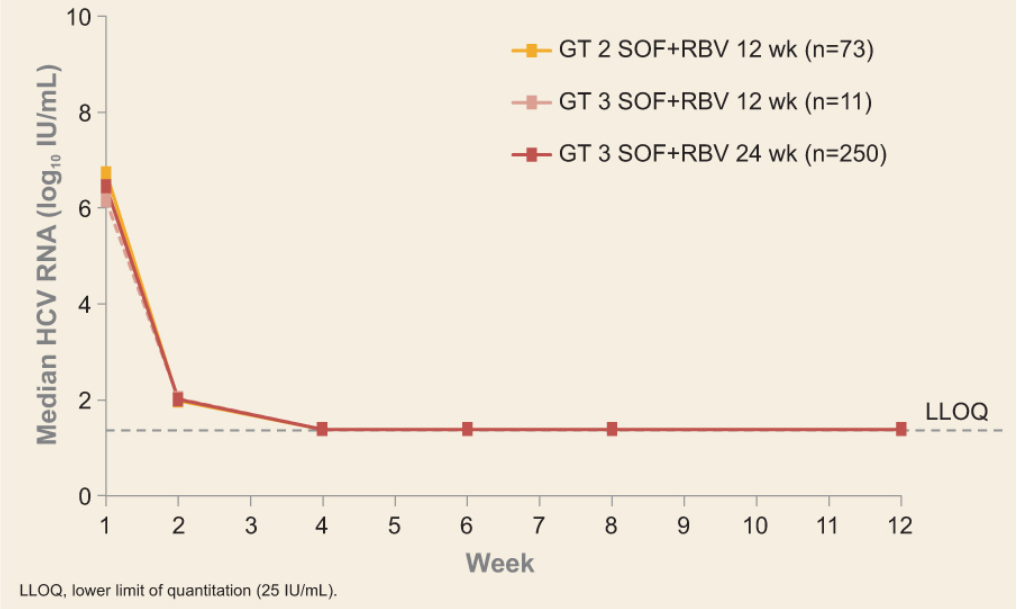
Figure 18: VALENCE - Viral kinetics (Zeuzem *et al.* 2013)[40]



HCV, hepatitis C virus; GT, genotype; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; wk, week.

Conclusion - VALENCE

In VALENCE, a double-blind, randomised, placebo-controlled study, patients with GT2 or GT3 HCV infection had a rapid response to SOF+RBV (within 4 weeks) with 100% of patients achieving HCV RNA < LLOQ at week 4.

In GT2 HCV-infected patients consistent with other studies, 12 weeks of treatment with SOF + RBV was associated with a high SVR12 rate (88 to 100%) irrespective of cirrhosis.

In GT3 HCV-infected patients, SOF + RBV for 24 weeks resulted in an SVR12 of 85%; treatment-naïve patients achieved rates >90% irrespective of cirrhosis status. GT3 treatment-experienced patients achieved SVR12 rates of 85% and 60% in the absence or presence of cirrhosis.

Extending duration to 24 weeks improved response in GT3 patients and was as well tolerated as 12 weeks of therapy with no additional adverse events.

These data clearly support the recommended duration of 24 weeks for all oral IFN-free therapy with SOF + RBV in those GT3 patients who are unsuitable for a 12 week IFN based regimen of SOF + PEG-IFN-2a + RBV.

6.5.3.2 Phase 2 studies

The following Phase 2 studies are included as they were used to design of the Phase 3 studies and provide supportive ormation during the regulatory process and SmPC recommendations. QUANTUM, PROTON, ATOMIC and ELECTRON also identified the once-daily dose of sofosbuvir to be taken forward into the Phase 3 programme and provided the first efficacy and safety data across different genotypes.

HCV GT2/3 treatment-experienced (IFN failure): Study GS-US-334-10151 (LONESTAR-2)

Study GS-US-334-0151 (LONESTAR-2)	
Citation	Lawitz *et al*. 2013c[44]. Additional information from clinical study protocol [43]
Objectives	LONESTAR-2 was designed to evaluate the efficacy and safety of SOF + PEG-IFN + RBV in patients with HCV GT2 or GT3 who had previously failed treatment with PEG +I FN and RBV therapy (treatment-experienced).
Location	The study was conducted at one site in the United States.
Design	Phase 2, single centre, open-label study of SOF + PEG-IFN-2a + RBV administered for 12 weeks.
Treatment period	12 weeks.

Key inclusion criteria and exclusion criteria	<u>Inclusion criteria</u>
	• ≥ 18 years of age
	• Chronic HCV GT2 or GT3 infection, documented by HCV RNA level ≥ 10,000 IU/mL during screening and either:
	  ○ a positive anti-HCV antibody test, a positive HCV RNA test or a positive HCV genotyping test ≥ 6 months prior to the Baseline/Day 1 visit; or
	  ○ a liver biopsy prior to the Baseline/Day 1 visit with evidence of chronic HCV infection
	• Patients had to be treatment experienced (defined as virologic failure with prior interferon-based treatment)
	• Compensated cirrhosis was permitted in approximately 50% of patients.
	  ○ presence of cirrhosis: positive liver biopsy or FibroTest® score >0.75 AND an APRI of >2 performed during screening
	  ○ absence of cirrhosis: negative liver biopsy,or FibroTest® score ≤0.48 AND an APRI of ≤1 performed during screening
	• Liver imaging within 6 months of baseline/day 1 to exclude hepatocellular carcinoma was required in patients with cirrhosis.
	• ≥ BMI of 18 kg/m^2
	<u>Exclusion criteria</u>
	• Prior exposure to a direct-acting antiviral targeting the HCV NS5B polymerase
	• Pregnant or nursing female or male with pregnant female partner
	• Co-infected with HBV or HIV
	• Chronic liver disease of a non-HCV aetiology
	• History or current evidence of clinical hepatic decompensation
	• HCC or other malignancy (with exception of certain resolved skin cancers)

Study GS-US-334-0151 (LONESTAR-2)	
	• History of clinically significant haemoglobinopathy, psychiatric conditions, drug/alcohol abuse, solid organ transplantation, pulmonary disease, significant cardiac disease or porphyria • Chronic use of immunosuppressive agents or immunomodulatory agents • History or current evidence of any condition, prohibited concomitant therapy, laboratory abnormality or other circumstance that might interfere with treatment, assessment, or compliance with study protocol
Treatment	SOF + PEG-IFN-2a +RBV for 12 weeks: SOF 400 mg OD + PEG-IFN-2a (subcutaneous 180 µg/week) + RBV (weight-based 1,000–1,200 mg/day as a daily divided dose).
Efficacy outcomes	The primary efficacy outcome was the proportion of patients with a SVR 12 weeks after the end of treatment. Secondary endpoints included proportion of patients who attained SVR at 4 weeks and 24 weeks after discontinuation of therapy (SVR4 and SVR24). Additional efficacy endpoints included viral kinetic parameters and evaluation of the emergence of viral resistance to sofosbuvir during treatment and after treatment discontinuation.
Populations analysed	FAS population: All patients randomised and who received at least one dose of study drug and have HCV RNA GT2 or 3. Safety population: All patients who received at least one dose of study drug.
Statistical information	Primary analysis of the primary outcome was performed in the FAS population. In general, missing data were not imputed. However, for categorical efficacy endpoints, if a data point was missing, and was preceded and followed by values that were deemed successes, then the missing data point was termed a success; otherwise the data point was termed as a failure. Any subject with missing data due to premature discontinuation of the study medication was considered a failure at the time points on, or following, the date of discontinuation. If no HCV RNA values were obtained after the last dose of study medication, the subject was considered a treatment failure for the SVR endpoints. *Primary hypothesis under investigation, statistical test and power calculation* In the primary efficacy analysis the SVR12 rate was calculated with the two-sided 95% exact confidence interval using the binomial distribution. No statistical hypothesis testing was performed. *Secondary analyses of the primary efficacy outcome* The study protocol stated that additional efficacy evaluations would be performed, including the proportion of patients who experience virologic failure and other endpoints of interest such as ALT normalisation, serum HCV RNA absolute values and change from baseline. Exploratory analyses of SVR12 may also be performed for various pre-specified demographic and baseline clinical characteristics and predictive factors of antiviral activities may be examine using regression type of analysis.

Study GS-US-334-0151 (LONESTAR-2)	
Patient disposition	In total, 47 patients received treatment with SOF + PEG-IFN-2a + RBV and were evaluated for the SVR12 endpoint. Treatment was completed by 44 patients.

Characteristic	GT2 SOF+PEG+RBV 12 weeks (N=23)	GT3 SOF+PEG+RBV 12 weeks (N=24)	Total SOF+PEG+RBV 12 weeks (N=47)
Patients in FAS, n	23	24	47
Study treatment status, n (%)			
Completed study treatment	22 (96)	22 (92)	44 (94)
Discontinued study treatment	1 (4)	2 (8)	3 (6)
Reason for treatment discontinuation, n (%)			
AE	0	1 (4)	1 (2)
Lost to follow up	0	1 (4)	1 (2)
Non-compliance	1 (4)	0	1 (2)

AE, adverse event; FAS, full analysis set; PEG, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir.

Patient demographics and baseline characteristics

The demographic and baseline clinical characteristics of the patients are provided below. Patients had a mean age of 56 years, 68% were male and the majority were white (96%). Cirrhosis was present in 55% of patients and 51% of patients had GT3 HCV infection.

Characteristic	SOF+PEG+RBV 12 weeks (N=47)
Mean age, year (range)	56 (39-72)
Mean BMI, kg/m^2 (range)	31 (21-53)
Male sex, n (%)	32 (68)
Race, n (%)	
White	45 (96)
Hispanic/Latino	21 (45)
HCV GT, n (%)	
2	23 (49)
3	24 (51)
Mean baseline HCV RNA, $\log_{10}$ IU/mL (range)	6.2 (4.0-7.2)
IL28B CC, n (%)	17 (36)
Cirrhotic liver, n (%)	26 (55)
Prior relapse/breakthrough, n (%)	40 (85)

GT, genotype; HCV, hepatitis C virus; PEG, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir;

Efficacy results

Primary efficacy outcome: The proportion of patients with SVR12

In patients with HCV GT2 or GT3 who had previous virologic failure with IFN based treatment, SVR12 was achieved in 89%. A total of 96% and 83% of patients with GT2 HCV infection and GT3 HCV infection achieved SVR12, respectively. Of the five patients who did not achieve SVR12, one discontinued with HCV RNA > LLOQ (GT2 group), two relapsed (GT3 group), and two were lost to follow-up (GT3 group).

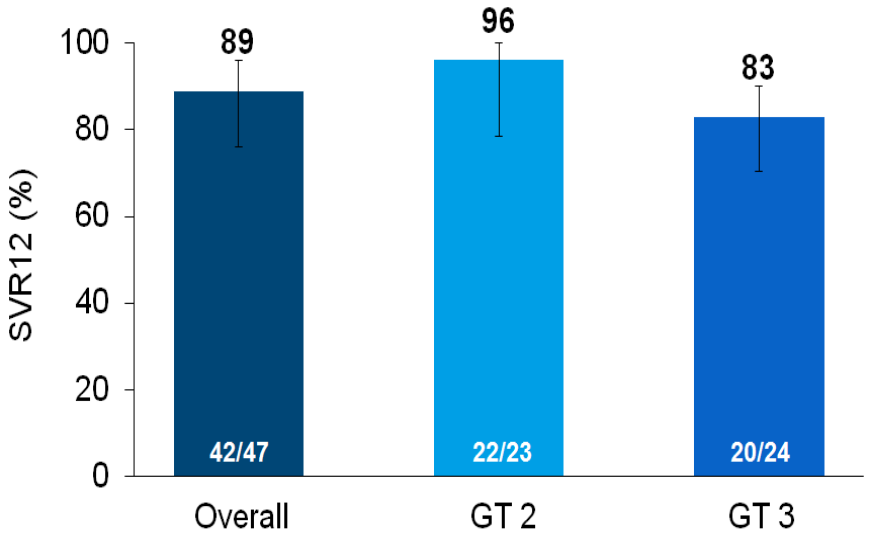
LONESTAR-2: SVR12 overall and by cirrhosis

Study GS-US-334-0151 (LONESTAR-2)

SVR12, n (%)		GT3 SOF+PEG+RBV 12 weeks (N=24)	Total +RBV 12 weeks (N=47)
Overall	22/23 (96)	20/24 (83)	42/47 (89)
By cirrhosis status			
With cirrhosis	13/14 (93)	10/12 (83)	-
Without cirrhosis	9/9 (100)	10/12 (83)	-

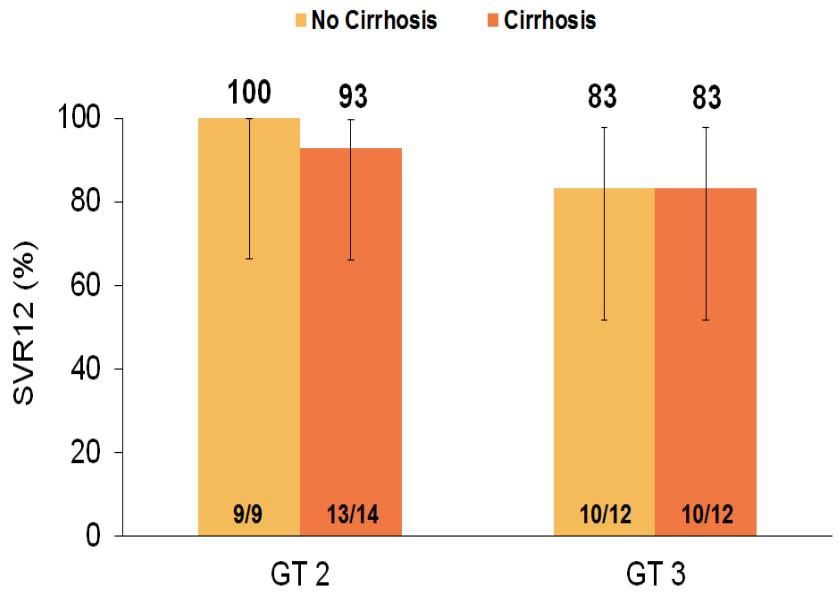
PEG, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR12, sustained virologic response at Week 12.

LONESTAR-2: Percentage of patients achieving SVR12



GT, genotype; SVR12, sustained virologic response at Week 12.

Presence of cirrhosis did not greatly affect the rate of SVR12 in GT2 patients (100% vs 93% for no cirrhosis) or GT3 patients (83% with and without cirrhosis)

Study GS-US-334-0151 (LONESTAR-2)	
	 GT, genotype; SVR12, sustained virologic response at Week 12. ***Secondary efficacy outcomes*** No further outcomes have been reported at this time.
Conclusion	In the VALENCE study 90% of GT2 and 77% of treatment-experienced patients achieved an SVR12 following 12 and 24 weeks respectively of an all oral regimen of SOF + RBV. The LONESTAR-2 study aimed to evaluate the efficacy of a 12 week SOF + PEG-IFN-2a + RBV regimen in treatment experienced patients with HCV GT2 an GT3, including those with cirrhosis. This Phase 2, single centre, open-label study, SOF + PEG-IFN-2a + RBV administered for 12 weeks, demonstrated high efficacy in treatment-experienced GT2 or GT3 HCV-infected patients who had historically low response rates and limited treatment options. Eight three percent (n=20/24) of GT3 patients achieved SVR12. Over half the patients had compensated cirrhosis with SVR12 rates similar in patients both with and without cirrhosis. This study included small numbers of patients but (in combination with PROTON and ELECTRON) supports the use of 12 weeks of SOF + PEG-IFN-2a as the recommended interferon-containing regimen for the treatment of treatment-naïve and treatment-experienced GT3 patients.

HCV GT1/2/3/4 Treatment naive: Study P2938-0721 (QUANTUM)

Study P2938-0721 (QUANTUM)	
Citation	Interim Clinical Study Report[45], final Clinical Study Report (retreatment group)[46] , Lalezari *et al*. 2013 [47]
Objectives	To investigate efficacy and safety of treatment regimens in treatment-naïve patients with chronic HCV infection. Although the study assessed both SOF and another experimental treatment (GS-0938), and patients with HCV of any HCV genotype were eligible, only SOF + RBV treatment groups are reported here and in these treatment groups HCV GT1/2/3 were represented.
Location	29 centres in the USA (SOF groups only)
Design	A Phase 2 blinded, randomised study in HCV treatment-naïve patients with or without cirrhosis. Approximately 50 treatment-naive patients with chronic HCV infection were randomised in equal ratios to the SOF groups, stratified by genotype, HCV RNA, and cirrhosis. Treatment groups were as follows: • Group C: SOF 400 mg and RBV weight based (1,000–1,200 mg) for 12 weeks • Group G: SOF 400 mg and RBV weight based (1,000–1,200 mg) for 24 weeks Due to an ALT signal related to GS-0938 all subjects who were randomised to other treatment regimens containing GS-0938 were required to discontinue all treatment in December 2011. These patients were followed off treatment for 12 weeks (safety follow-up period) and if eligible (based on ALT and HCV RNA levels and consenting, patients were retreated with SOF + RBV for 24 weeks and then followed off treatment for 24 weeks. These patients comprised the retreatment group.
Treatment period	12–24 weeks depending on treatment group
Key inclusion criteria and exclusion criteria	This study enrolled treatment-naive male and non-pregnant, non-lactating female patients with HCV infection. Patients were ≥18 years of age and had a BMI ≥18 kg/m^2. Patients had HCV RNA levels ≥ 50,000 IU/mL at screening. Up to 10% of patients were allowed to have evidence of cirrhosis (Child-Pugh-Turcotte Classification A only) at screening. Patients also had neutrophil count ≥ 1,500 cells/mm^3 (or ≥ 1,250 cells/mm^3 for African American/black patients); haemoglobin ≥ 11 g/dL in females or ≥ 12 g/dL in males; and platelet count ≥ 50,000 cells/mm^3.
Efficacy outcomes	Primary efficacy endpoint was SVR12 based on a HCV RNA level of <25 IU/mL (LLOQ). Secondary endpoints HCV RNA levels at various time points during and after the end of treatment and assessment of virologic failure.
Populations analysed	Efficacy analysis set consisted of all patients randomised to groups C and G and received at least one dose of study drug.
Statistical information	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

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<tr><td>Patient disposition</td><td>XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

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<tr><td>Patient demographics and baseline characteristics</td><td>Overall, the demographic characteristics were XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

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Retreatment group

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<tr><td>Efficacy results</td><td>XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXX SVR12 rates were observed for patients with HCV GT1 infection (53% [10/19] and 47% [9/19], respectively). XXXXXXXXXXXXXXXXXXXXXXXXX

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<tr><th rowspan="2"></th><th rowspan="2">SOF+RBV 12 weeks (n=25)</th><th rowspan="2">SOF+RBV 24 weeks (n=25)</th><th colspan="2">Between group difference</th></tr>
<tr><th>P-value</th><th>Proportional difference (95% CI)</th></tr>
<tr><td>SVR12</td><td>XXXXXX</td><td>XXXXXX</td><td>XXXX</td><td>XXXXXXXXX</td></tr>
<tr><td colspan="5">Virologic failure</td></tr>
<tr><td>On-tx</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Post-tx relapse</td><td>XXXXX</td><td>XXXXX</td><td>X</td><td>X</td></tr>
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Study P2938-0721 (QUANTUM)	
	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
Conclusion	In QUANTUM, a Phase 2 study, SOF + RBV for 12 and 24 weeks resulted in XXXXXXXXX in treatment naïve patients with HCV GT1/2/3 (76% GT1). SVR12 was achieved in XXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. SVR12 was achieved in XXX of patients in the re-treatment group treated with SOF+RBV for 24 weeks

HCV GT1, treatment-naive, difficult-to-treat patients: STUDY 11-1-0258 (SPARE)

STUDY 11-1-0258 (SPARE)	
Citation	Osinusi *et al*, 2013 and 2012[48;52]
Objectives	The SPARE trial was designed to assess the efficacy and safety of sofosbuvir and weight-based or low dose RBV in patients with HCV GT1 HCV infection who had unfavourable treatment characteristics.
Location	Single centre (USA)
Design	Phase 2, randomised, 2-part trial in HCV treatment-naïve patients with HCV GT1. In part 1 (proof of concept), patients with early to moderate liver fibrosis (Knodell histology activity index fibrosis score, 0–1) were sequentially enrolled in an open-label group and treated for 24 weeks with SOF 400 mg once daily and weight-based RBV (1,000–1,200 mg split into two daily doses). In part 2, eligible patients with all stages of fibrosis (including compensated cirrhosis) were randomised to receive SOF 400 mg once daily in combination with either weight-based RBV or low-dose (600 mg/day) RBV for 24 weeks. Randomisation was performed using a set of 60 random numbers, in which blocks of 4 numbers were selected. Within a block, the highest numbers were assigned to the weight-based protocol, and the lower numbers were assigned to the low-dose group. Upon enrolment patients received a study number in sequential fashion. Patients experiencing treatment failure were offered the current standard of care.
Treatment period	24 weeks depending on treatment cohort
Key inclusion criteria and exclusion criteria	Eligible participants were infected with HCV GT1, had liver biopsy-proven chronic disease, and were naive to HCV treatment. Additional criteria included seronegativity for HIV and HBV; absolute neutrophil count ≥ 750 cells/µL; platelet count ≥ 50,000 cells/µL; haemoglobin ≥ 11 g/dL for women and ≥ 12 g/dL for men. Race/ethnicity was classified as white, black, or Hispanic using patient self-reported data.
Efficacy outcomes	Primary endpoint was the proportion of patients with undetectable HCV viral load 24 weeks after treatment completion (SVR24). Secondary endpoints included the proportion of patients with undetectable HCV viral load at specified time points during and after treatment. Plasma HCV RNA levels were measured at all time points for efficacy outcomes by way of assay with a LLOQ of 43 IU/mL and LLOD of 12 IU/mL.
Populations analysed	Although the primary interest was the per-protocol analysis, ITT analysis of all randomised patients was also included because these results are more readily generalisable. Per-protocol analysis included all patients who received ≥ 8 weeks of study drug. For efficacy analysis, missing data points were

STUDY 11-1-0258 (SPARE)	
	deemed a success if the immediately preceding and subsequent time points were successful; otherwise, data points were termed as failures. Participants who had missing data due to premature discontinuations were considered failures from the point of discontinuation.
Statistical information	Comparisons were analysed using the non-parametric Wilcoxon rank sum test for continuous outcomes and Fisher exact test for binary outcomes. A bivariable logistic regression model of baseline characteristics was used to identify factors associated with relapse. All p values were 2-tailed and were considered significant when <0.05. Sample size was calculated using an assumed early response rate of 90% for the weight-based RBV group vs. 85% for the low-dose RBV group. With 50 patients, the study was powered to estimate a difference in early virologic response proportions to within ±0.18. There was a substantial gain in precision (from an accuracy of ±0.24 to ±0.18) by increasing sample size from 15 to 25 per group but diminishing returns beyond a sample size of 25.
Patient disposition	79 patients were screened and 60 were enrolled in this study, including 10 in part 1 (proof of concept) and 50 in part 2 (randomised). Part 1: one patient was lost to follow up. Part 2: in the weight-based RBV group, one patient was lost to follow up and one patient discontinued treatment; in the low dose group one patient was lost to follow up and two discontinued treatment.
Patient demographics and baseline characteristics	Baseline characteristics were similar among treatment groups. 83% were black; 66% were men; 48% had a BMI >30; 81% had non-CC IL28B genotype; 70% had GT-1a infection; 23% had advanced liver disease; and 62% had baseline HCV RNA levels >800,000 IU/mL.
Efficacy results	In part 1 90% (n=9) of patients infected with GT1 HCV and treated with SOF + RBV weight-based for 24 weeks achieved SVR24. In part 2, 24 patients infected with GT1 HCV in each group (96%) achieved viral suppression by Week 4 of treatment. Seven and ten patients in the weight-based and low dose groups, respectively, relapsed after treatment completion leading to SVR12 and SVR24 rates of 68% and 48%.

HCV RNA <LLOQ	SOF+RBV WB (n=25)		SOF+RBV LD (n=25)	
	ITT	PP	ITT	PP
During treatment				
4 weeks	24 (96)	24 (96)	24 (96)	24 (96)
8 weeks	24 (96)	24 (100)	22 (88)	22 (100)
24 weeks	24 (96)	24 (100)	22 (88)	22 (100)
Post-treatment				
SVR12	17 (68)	17 (71)	12 (48)	12 (55)
SVR24	17 (68)	17 (71)	12 (48)	12 (55)

ITT, intention-to-treat; LD, low dose RBV (600 mg/day); PP, per protocol; RBV, ribavirin; SVR12, sustained virologic response at Week 12 after treatment; SVR24, sustained virologic response at Week 24 after treatment; tx, treatment; WB, weight-based RBV (1,000–1,200 mg/day).

STUDY 11-1-0258 (SPARE)	
	Data are n (%). Treatment responses in all patients were included in ITT analysis. Those who completed ≥8 weeks of treatment were included in the PP analysis. The PP analysis excludes all patients who stopped study medication for non-adherence to protocol (1 patient in the WB group at Week 3, 3 patients in LD group by Week 8).
Conclusion	In the phase 2 SPARE study, 24 weeks of treatment with SOF + RBV resulted in a high rate of SVR 12 (68%) in patients with GT1 HCV infection. These patients had a high prevalence of traditional negative predictors for unfavourable treatment outcome, including black race, HCV GT1a, advanced fibrosis, IL-28B non-CC genotype and high BMI and are viewed as the most difficult-to-treat populations.

HCV GT1/2/3, treatment naive: P7977-0422 (PROTON)

Study P7977-0422 (PROTON)	
Citation	Lawitz *et al*, 2013[53]. Additional information from clinical study report[54].
Objectives	To assess safety and tolerability of: ○ two doses of SOF (200 mg; 400 mg) plus PEG-IFN-2a + RBV in patients with HCV GT1 and; ○ SOF 400 mg plus PEG-IFN-2a + RBV in a separate, open-label cohort of patients with HCV GT2 and GT3. Efficacy was also assessed although the trial was not designed to statistically assess efficacy. Only data from the GT2/3 cohort has been used to inform the regulatory application for sofosbuvir and hence the GT1 cohort is not presented here.
Location	22 centres in the USA
Design	Phase 2, two cohort trial in HCV treatment naïve patients with HCV GT1/2/3 who were eligible for IFN treatment and without cirrhosis. • Cohort A was the GT1 cohort and is not presented here • In cohort B (GT2/3) patients received open-label SOF 400 mg plus PEG-IFN-2a + RBV for 12 weeks.
Treatment period	GT1: 12 weeks followed by a further 12 or 36 weeks GT2/3: 12 weeks
Key inclusion criteria and exclusion criteria	Patients with HCV GT1–3 and an HCV RNA ≥ 50,000 IU/mL were eligible for inclusion. HCV genotypes/sub-types were assessed at an independent laboratory. Patients had a liver biopsy ≤ 36 months before enrolment; those with cirrhosis were excluded from the trial. Inclusion criteria also included: neutrophil count of $1{\cdot}5\times10^9$/L (or ≥ $1{\cdot}25\times10^9$/L for black patients), haemoglobin concentration of ≥ 11 g/dL in women or ≥ 12 g/dL in men, platelet count of >90 × 10^9/L, total bilirubin within 2 x ULN (21 µmol/L), and an albumin concentration of <30 g/L. Patients with HBV or HIV, psychiatric illness, pulmonary or cardiac disease, seizure disorder, or other serious comorbid disorders were excluded.
Permitted and disallowed concomitant medications	Use of erythropoietin-stimulating agents or GCSF was permitted to manage anaemia at the treating clinician's discretion only after the 12 weeks of sofosbuvir or placebo dosing.
Outcomes	Safety was the primary outcome in this trial. Efficacy outcomes included: rapid viral response (RVR; defined as HCV RNA <15 IU/mL at Week 4 of treatment); eRVR (defined in "Design"), response at end of treatment; and SVR12 and SVR24 (HCV RNA <15 IU/mL 12 weeks and 24 weeks after the end of treatment).
Populations analysed	All randomly allocated patients who received ≥ one dose of study drug were included in all efficacy and safety analyses.
Patient disposition	Cohort B: 25 patients randomised to SOF + PEG-IFN-2a + RBV. One patient was lost to follow up.
Patient demographics and baseline characteristics	Across the entire study population the mean age of patients was about 50 years and most patients were men, white, non-Hispanic, had the IL28B CC or CT genotype, and had portal fibrosis. Most patients in Cohort A had GT1a HCV and mean baseline HCV RNA concentrations across the study were around 6.5 $\log_{10}$ IU/mL.

Study P7977-0422 (PROTON)	
	Baseline characteristics (other than HCV genotype) were much the same between individuals in cohort A and cohort B. In Cohort B 40% (n=10) had GT3 infection.
Efficacy results	SVR12 was achieved by 92% (23/25) of patients with GT2/3 infection (Cohort B) a) 93% in patients (14/15) with GT2 infection b) 90% of patients (9/10) with GT3 HCV infection No patient suffered from virologic breakthrough during SOF treatment, or in the period following treatment.

	Cohort B (GT2/3)
	SOF 400 mg+PEG+RBV n=25
RVR (4 weeks)	24 (96)
eRVR (12 weeks)	24 (100)
Response at EoT	24 (100)
SVR12	23 (92)
SVR24†	23 (92)
Virologic failure	
Rebound or breakthrough	0
Post-treatment relapse	0

EoT, end of treatment; PEG, peginterferon; RBV, ribavirin. (e)RVR, (extended) rapid virologic response; SVR12, sustained virologic response at week 12 after treatment; SVR24, sustained virologic response at week 24 after treatment; tx, treatment. Data are n (%). †Two patients from the 200 mg group and one from the 400 mg group who achieved SVR12 had missing values for post-treatment week 24 – sensitivity analysis in which these three patients were excluded from the denominator of the SVR24 estimate resulted in 41 of 46 patients (89%, 95% CI 76–96%) in the 200 mg group and 42 of 46 patients (91%, 95% CI: 79–98%) for the 400 mg group achieving SVR24.

Conclusion	PROTON (Phase 2) demonstrated that 12 weeks of treatment with SOF + PEF-IFN-2a+RBV is highly efficacious in the treatment of patients infected with HCV GT1, 2 and 3, supporting the recommended duration of treatment when sofosbuvir triple therapy is used. In these GT2- and GT3-infected, treatment naïve, non-cirrhotic patients, SVR12 rates ≥90% were observed.

HCV GT1/2/3, treatment-naïve or treatment-experienced (inteferon failures): Study GS-US-337-0122 (ELECTRON)

Study GS-US-337-0122 (ELECTRON)	
Citation	Gane *et al*, 2013[57]
Objectives	The ELECTRON trial was designed to assess the efficacy and safety of SOF + RBV in various) interferon (IFN)-sparing and IFN-free regimens in treating HCV GT1/2/3 infection in treatment-naïve and -experienced patients. Only data from the GT2/3 cohort has been used to inform the regulatory application for sofosbuvir, and hence the GT1 cohort is not presented within this submission. Similarly, sofosbuvir monotherapy does not form part of the sofosbuvir licence and hence GT2/3 patients randomised to sofosbuvir monotherapy are not presented here.
Location	2 centres in New Zealand

Design	Phase 2, randomised, open-label trial in HCV treatment-naïve (IFN eligible) and treatment-experienced patients (IFN treatment failures) with HCV GT1/2/3 and without cirrhosis. Patients were randomised to one of eight treatment groups.
	• Treatment naïve GT2/3:
	  ○ Four groups of patients (randomised 1:1:1:1) all received SOF + RBV for 12 weeks and either 0, 4, 8 or 12 weeks of PEG
	  ○ One group received SOF + PEG-INF-2a + RBV for 8 weeks (added as a protocol amendment after completion of four dosing groups above).
	  ○ One group received SOF monotherapy for 12 weeks and are not presented here (added as a protocol amendment as above).
	• Groups 7 and 8 were in GT1 patients and are not presented here.
	Doses across all treatment groups were: SOF 400 mg once daily; RBV (weight based 1,000–1,200 mg, split into two daily doses); PEG-INF-2a (180 µg per week subcutaneously).

Treatment period	8 or 12 weeks depending on treatment group
Key inclusion criteria and exclusion criteria	Eligible patients were men and women, ≥ 18 years of age, with chronic HCV infection (serum HCV RNA level, >50,000 IU/mL) and without cirrhosis. The absence of cirrhosis was determined either by means of liver biopsy within the previous 3 years or by means of transient elastography within the previous 12 months. Patients with positive tests for HBV surface antigen, HBV core IgM antibodies, or antibodies against HIV were excluded. Prescribed maintenance therapy with methadone was allowed.
Efficacy outcomes	Endpoints included virologic response at time points during and after the end of treatment. The LLOD for HCV RNA was 15 IU/mL. Time points of HCV RNA measurements included screening, baseline, 6, 12, 24, 48, and 72 hours after the first dose, weekly throughout the 8-week or 12-week treatment period, and 2, 4, 8, 12, and 24 weeks after treatment.
Statistical information	This study was not designed to evaluate formal statistical hypotheses, and no sample-size calculations were performed. The magnitude of decline in HCV RNA level, and rates of virologic response during and

Study GS-US-337-0122 (ELECTRON)	
	after treatment were descriptively compared across the treatment groups. For virologic response, two-sided 95% CIs were calculated with the use of the exact binomial distribution
Patient disposition	95 patients were enrolled and received at least one dose of study drug. All patients completed treatment with SOF + RBV. One patient discontinued PEG in the GT2/3 SOF + PEG-IFN-2a + RBV 12 week group.
Patient demographics and baseline characteristics	Across the five GT2/3 study arms considered here, ranging in size between 9 and 11 patients, the mean age ranged between 39 and 49 years, 50–82% of patients were male and 44–82% were white. Median baseline HCV RNA log_{10} ranged between 6.0 and 6.7 IU/mL and the majority of patients had a non-CC IL28B genotype.
Efficacy results	○ In patients with GT2/3 infection, 100% response was achieved in all treatment groups by Week 4 and maintained throughout treatment. ○ SVR12 and SVR24 was achieved by all patients (100%) following treatment with SOF+RBV (group 1) or SOF + PEG-IFN-2a + RBV (group 2–4 and group 6). ○ Across these groups 6, 6, 6, 7 and 10 patients, respectively had GT3 infection and achieved SVR12/24 (all 100%)
Conclusion	The Phase 2 ELECTRON study demonstrated that GT2 or GT3 treatment-naïve non-cirrhotic patients treated with 12 weeks of SOF + RBV plus 0-12 weeks of PEG-IFN-2a achieved 100% SVR12. Reducing treatment duration to less than 12 weeks or decreasing RBV dose reduced treatment efficacy.

HCV GT1/4/5/6, treatment naive: Phase 2 Study P7977-0724 (ATOMIC)

Study P7977-0724 (ATOMIC)	
Citation	Kowdley *et al.* 2013[55]
Objectives	The ATOMIC trial was designed to assess whether a 12-week regimen of SOF + PEG-IFN + RBV is as effective as a 24-week regimen. In addition, it explored whether 12 weeks of SOF + PEG-IFN-2a + RBV followed by an additional 12 weeks of SOF monotherapy or SOF + RBV offers any benefit compared with the 12-week regimen of SOF + PEG-IFN-2a + RBV.
Location	42 centres in the USA and Puerto Rico
Design	Phase 2, randomised, open-label trial in HCV treatment-naïve patients with HCV GT1/4/5/6 who were eligible for IFN treatment and without cirrhosis. Patients with HCV GT1 were randomised to one of three cohorts (A, B, and C, in a 1:2:3 ratio). Patients received SOF 400 mg plus PEG-IFN-2a (180 µg per week subcutaneously) and RBV (weight-based dosing: 1,000–1,200 mg daily) for 12 weeks (cohort A) or for 24 weeks (cohort B), or 12 weeks of SOF + PEG-IFN-2a + RBV followed by 12 weeks of either sofosbuvir monotherapy (cohort C1) or SOF + RBV (cohort C2). Patients in cohort A who did not achieve RVR (defined as HCV RNA <15 IU/mL [LLOD] at Week 4) continued to receive SOF + PEG-IFN-2a + RBV for an additional 12 weeks. Patients with GT4/5/6 were enrolled into cohort B. Randomisation was performed using a computer-generated randomisation sequence and an interactive web-based response system. For the study to have been blinded, patients in cohorts A and C would have had to receive placebo for 12 weeks after the conclusion of their planned dosing, and it was decided that the potential benefits of blinding did not warrant the risk and inconvenience to patients.
Treatment period	12 or 24 weeks depending on treatment cohort
Key inclusion criteria and exclusion criteria	Eligible patients were ≥ 18 years of age, were HCV treatment naïve, and had chronic GT1/4/5/6 HCV infection with serum HCV RNA ≥ 50,000 IU/mL. Exclusion criteria included: histological evidence of cirrhosis (patients had to have had a liver biopsy done ≤ 36 months of entry) or other clinically important chronic liver disease; BMI ≤ 18 kg/m^2; co-infection with HBV or HIV. Patients with a history of psychiatric illness were eligible if approved by a psychiatrist or licensed mental health professional.
Efficacy outcomes	Primary efficacy endpoint: SVR (HCV RNA <15 IU/mL) 24 weeks after the end of treatment (SVR24), with the primary analysis comparing the proportion of patients achieving this outcome in each treatment group. Secondary endpoints included: proportion of patients with undetectable HCV RNA at all time points throughout the study, including RVR (after 4 weeks of treatment) and SVR12.

Study P7977-0724 (ATOMIC)	
Populations analysed	The ITT analysis included all patients who were enrolled and received ≥ 1 dose of study drug.
Statistical information	For SVR24 point estimates and two-sided 95% CIs of between-group differences were calculated using stratum-adjusted Mantel-Haenszel proportions. Secondary endpoints are provided as point estimates and exact 95% CIs. It was estimated that a sample size of 50 patients and 100 patients or a sample size of 75 patients and 100 patients would be sufficient to achieve 90% power to detect a 30% or 25% difference in SVR24 rates between two treatment groups with the χ^2 and a 5% two-sided significance level.
Patient disposition	332 patients were enrolled. No patients with GT5 were enrolled. Cohort A: 52 patients randomised, 5 patients discontinued treatment. Cohort B: 125 patients randomised; GT1 (n=109), GT4 (n=11), GT6 (n=5). 27 patients discontinued treatment. Cohort C: 155 patients randomised, 5 patients discontinued treatment in the initial 12-week treatment period with SOF + PEG + RBV. Following assignment to sofosbuvir monotherapy (n=75) or SOF + RBV (n=75) for an additional 12 weeks, 7 and 3 patients, respectively discontinued treatment Differences in discontinuation between cohort A and B were driven mainly by adverse events; 3 and 18 patients discontinued treatment due to AEs in cohort A and B, respectively.
Patient demographics and baseline characteristics	Baseline characteristics were similar across the three treatment cohorts. Across the entire study population the mean age of patients was about 50 years and most patients were men, white, non-Hispanic or non-Latino, had a non-CC IL28B genotype, and had portal fibrosis. Most patients had GT1a HCV infection (n=241) and the mean baseline HCV RNA concentrations across the study were around 6.5 $\log_{10}$ IU/mL.
Efficacy results	

	Cohort A SOF+PEG+RBV 12 weeks n=52	Cohort B SOF+PEG+RBV 24 weeks n=109	Cohort C¶ SOF+PEG+RBV 12 weeks then SOF mono or SOF+RBV 12 weeks n=155
RVR (4 weeks)	49 (94)	107 (98	151 (97
SVR12	47 (90)	101 (93)	141 (91
SVR24 (ITT analysis)	46 (89)	97 (89)	135 (87)
SVR24 (PP analysis)†	46/48 (96)	97/99 (98)	135/139 (97)
Virologic failure			
During tx‡	0	0	0
Relapse§	2 (4%)	1 (1%)	4 (3%)

ITT, intention-to-treat; PEG, peginterferon; RBV, ribavirin. RVR, rapid virologic response (undetectable HCV RNA at Week 4); SVR12, sustained virologic response at Week 12 after treatment; SVR24, sustained virologic response at Week 24 after treatment; tx, treatment. Data are n (%) or n/N (%). †Missing data were excluded from analysis; ‡Includes virologic

Study P7977-0724 (ATOMIC)	
	breakthrough, rebound, and non-response; §Includes only those patients who completed the full course of assigned treatment; ¶Efficacy results for patients in cohort C who were randomly allocated into two subgroups for the second 12 weeks of treatment – those who received sofosbuvir monotherapy (cohort C1) and those who received sofosbuvir/RBV (cohort C2) – were very similar, hence their data were pooled when assessing efficacy. High rates of SVR12 and SVR24 were observed in all three groups. There was no difference in the proportions of patients achieving SVR24 between cohorts A and B (p=0·94) or between cohorts A and C (p=0·78), suggesting no additional benefit of treatment durations of longer than 12 weeks in treatment naïve IFN eligible patients with HCV GT1. Factors shown to be associated with reduced response to treatment did not seem to greatly affect response to sofosbuvir. Rates of SVR24 for patients with particular characteristics were: 89% in cohort A, 90% in cohort B, and 87% in cohort C in those with high baseline HCV RNA (≥800 000 IU/mL); 87% in cohort A, 90% in cohort B, and 88% in cohort C for patients carrying non-CC IL28B genotypes; 100% versus 87% in cohort A, 88% versus 89% in cohort B, and 83% versus 88% for cohort C patients with bridging fibrosis versus those without bridging fibrosis. No patients had viral breakthrough during treatment. Of the 11 patients who had a return of detectable HCV RNA after stopping treatment, seven relapsed after completing their assigned treatment regimen. Although SVR24 rates were slightly lower than SVR12 rates this was due to loss to follow-up after 12 weeks not relapse. The other four patients with failure after the end of treatment did not complete their assigned course.
Conclusion	ATOMIC, a Phase 2, open-label, randomised study demonstrated high SVR12 and SVR24 rates (≥89%) following 12 weeks treatment with SOF + PEG-IFN-2a + RBV in treatment-naïve, non-cirrhotic patients with HCV GT1/4/6 infection. In this specific population there was no additional benefit to extending the SOF treatment duration beyond 12 weeks, and further supports the recommended 12-week duration of treatment when sofosbuvir triple therapy (SOF + PEG-IFN-2a + RBV) is used

6.5.3.3 Special populations

HCV/HIV co-infection (GT1/2/3): Study GS-US-334-0123 (PHOTON-1)

Co-infection with HCV is common in HIV-infected individuals. HIV co-infection exacerbates HCV disease, increasing the likelihood of cirrhosis and HCV-related mortality (Davies et al 2013, Taylor et al. 2012)[77;78]. Related to this, HCV has become the leading cause of death, after AIDS-related complications, in HIV-infected individuals treated with highly active antiretroviral therapy (Taylor et al. 2012)[78] Although peginterferon+ribavirin can be successful in patients with HCV/HIV co-infection, with SVR rates in GT2 and GT3 co-infected patients being similar to those in HCV mono-infected patients, in GT 1 and GT 4 patients SVR rates are relatively low compared with mono-infected patients (Davies et al 2013)[77]. The treatment of HCV/HIV co-infected patients is complicated by a range of factors, including the potential for drug-drug interactions between antiretroviral therapy and anti-HCV treatment (Davies et al 2013)[77]. Unlike other HCV treatments (such as the protease inhibitors) sofosbuvir has been shown to have no clinically relevant interactions with a range of different classes of antiretroviral therapy (See SmPC, Appendix 1.0) and as such offers patients the potential for a 12 week SOF + PEG-IFN + RBV regimen and also the potential for IFN-free treatment for HCV/HIV co-infected patients unsuitable for interferon.

Study GS-US-334-0123 (PHOTON-1)	
Citation	Sulkowski et al, 2013[41]. Additional information from interim clinical study report[42].
Objectives	PHOTON-1 is an on-going study designed to assess the efficacy and safety of SOF + RBV in patients with GT1, 2 or 3 HCV infection and HIV-1 co-infection.
Location	Multicentre study conducted in the USA and Puerto Rico.
Design	Ongoing Phase 3, open-label, multicentre study in HCV treatment-naïve patients with HCV GT1/2/3 and treatment-experienced patients with GT2/3 all co-infected with HIV-1. • Group 1: Treatment-naive patients with GT1 HCV infection received SOF + RBV for 24 weeks • Group 2 (a and b): Treatment-naive patients with GT2/3 HCV infection received SOF + RBV for 12 weeks (Note: Results are presented by GT for these patients) • Group 3: Treatment-experienced patients with GT2/3 HCV infection received SOF + RBV for 24 weeks (Note: 28 of 41 patients have completed post-treatment follow-up through to Week 12 or prematurely discontinued the study; data for these 28 patients only are presented in the efficacy analysis) Dosing was as follows in all groups: SOF 400 mg OD + RBV BID (according to bodyweight; a total of 1,000 [<75 kg] or 1,200 mg/day [≥75 kg] as a daily divided dose)
Treatment period	12 or 24 weeks depending on treatment cohort.
Key inclusion criteria and exclusion criteria	Eligible patients were males or non-pregnant females aged ≥18 years with chronic GT1/2/3 HCV infection and confirmed HIV-1 co-infection, treatment naive or treatment experienced, had documentation of cirrhosis presence/absence; and BMI ≥18 kg/m^2.

Study GS-US-334-0123 (PHOTON-1)	
	Patients on antiretroviral treatment were required to have >8 weeks on a stable regimen prior to screening, have HIV-1 RNA <50 copies/mL, and CD4 T-lymphocyte count >200 cells/mm^3. Regimens containing emtricitabine/tenofovir, atzanavir/ritonavir, darunavir/ritonavir, efavirenz, raltegravir, or rilpivirine were permitted. Patients not on antiretroviral treatment must have had a CD4 T-lymphocyte count >500 cells/mm^3 at screening.
Efficacy outcomes	Primary efficacy endpoint: SVR (HCV RNA <25 IU/mL) 12 weeks after the end of treatment (SVR12). Secondary endpoints included: proportion of patients achieving SVR4 and SVR24, kinetics of circulating HCV RNA, and emergence of viral resistance to SOF.
Populations analysed	Planned analysis is on the FAS population which patients who received ≥1 dose of study drug and who completed the post-treatment week 12 visit or prematurely discontinued from study. In the current analysis FAS includes all treatment-naive patients with GT1/2/3 HCV infection whereas data are only available for 28/41 treatment-experienced patients with GT2/3 HCV infection.
Statistical information	For SVR12 point estimates and two-sided 95% CIs were calculated for each treatment group.
Patient disposition	• Group 1 (GT1, Treatment-naive): 114 patients; 11/114 (10%) patients discontinued treatment • Group 2a (GT2, Treatment-naive): 26 patients; 3/26 (12%) patients discontinued treatment • Group 2b (GT3, Treatment-naive): 42 patients; 3/42 (7%) patients discontinued treatment • Group 3 (GT2/3, Treatment-exp): of 41 patients enrolled, 28 have completed post-treatment follow up through Week 12; 1/41 (2.4%) patients discontinued treatment
Patient demographics and baseline characteristics	Across the treatment-naïve groups baseline characteristics and demographics were similar: mean age 48-49; 81-82% male; mean BMI 27-28 kg/m^2; black 5-33%; Hispanic 22-31%; majority were non-CC IL28B genotype (61-73%); mean baseline HCV RNA $\log_{10}$ IU/mL 6.2-6.6; 4-14% had cirrhosis and 85-98% were on ART.
Efficacy results	

	Group 1 GT1, Tx-naive SOF+RBV 24 weeks n=114	**Group 2a GT2, Tx-naive SOF+RBV 12 weeks n=26**	**Group 2b GT3, Tx-naive SOF+RBV 12 weeks n=42**	**Group 3 GT2/3, Tx-exp SOF+RBV 24 weeks n=28**
HCV RNA <LLOQ, n/N (%)				
Week 4	110/114 (96)	25/26 (96)	41/41 (100)	-
EOT	103/103 (100)	22/23 (96)	39/40 (98)	-
SVR12	87/114 (76)	23/26 (88)	28/42 (67)	26/28 (93)
Virologic failure	25 (22)	1 (4)	12 (29)	2/28 (7)
Relapse	25 (22)	0	12 (29)	2/28 (7)
Breakthrough†	1 (<1)	1 (4)	0	0

†Both patients with HCV breakthrough were non-adherent to SOF, confirmed by PK analysis.

Study GS-US-334-0123 (PHOTON-1)	
	In addition to the tabulated results, sub-group analysis of treatment experienced patients (group 3) showed high SVR12 rates irrespective of genotype: GT2 93% (14/15); GT3 92% (12/13).
Conclusion	PHOTON-1, was a open-label, multicentre study Phase 3 study which investigated the efficacy of all-oral SOF + RBV in 182 treatment-naïve and 41 treatment-experienced patients with HCV/HIV confection • In HCV/HIV co-infection treatment-naïve patients with GT1/2/3 infection, SOF + RBV for 12 (GT2/3) or 24 (GT1) weeks resulted in high SVR12 rates which were similar to those reported for patients with HCV mono-infection. • In HCV treatment-experienced patients with GT2/3 infection, SOF + RBV for 24 weeks resulted in high SVR12 rates, irrespective of HCV genotype (≥93%; interim analysis). • SOF + RBV was effectively co-administered with multiple antiretroviral regimens including inhibitors of HIV-1 protease, reverse transcriptase (non nucleoside/nucleoside(and integrase inhibitors • Similar safety, efficacy and tolerability was observed in HIV/HCV co-infected patients compared to HCV mono-infected patients • Due to the findings that HIV/HCV co-infection patients respond to SOF based regimens with similar efficacy and safety results to those reported from mono-infected patients future studies for SOFwill now include HIV co-infected patients within the overall study population.

Pre-Liver Transplant (Any GT): Study P7977-2025

In patients who are serum HCV RNA-positive at the time of liver transplantation re-infection of the transplanted liver with HCV is universal and immediate. HCV recurrence in these patients can result in accelerated progression to cirrhosis, graft failure and death. However, recurrent infection is rare if HCV RNA has been eradicated prior to transplant. As such effective treatment of HCV infection prior to transplant is necessary.

Study P7977-2025 Pre-liver transplant	
Citation	Curry et al.2013[62] Additional information from study protocol[79]
Objectives	This on-going trial was designed to determine if the administration of SOF + RBV prior to undergoing liver transplant can prevent post-transplant reinfection.
Location	16 centres
Design	Phase 2, single arm, open-label trial in patients with HCV (any genotype) awaiting liver transplant. Patients were treated with SOF400 mg+RBV (weight-based, 1,000–1,200 mg).
Treatment period	Treatment duration was defined in the original protocol as until liver transplant or up to 24 weeks. A protocol amendment extended possible treatment duration to up to 48 weeks.
Key inclusion criteria and exclusion criteria	Eligibility criteria included: males or females, aged ≥18 years, with HCV and HCC meeting MILAN criteria; standardized immunosuppressive regimen for the first 12 weeks post-transplant (tacrolimus/ mycophenolate mofetil/ prednisone). Patients were excluded for the following reasons: living donor liver transplantation; planned induction therapy with biologics; signs of decompensated cirrhosis; HBV or HIV coinfection; history of prior solid organ transplantation; evidence of renal impairment (CrCl <60 mL/min)
Efficacy outcomes	Primary endpoint is post-transplant virologic response (pTVR; HCV RNA <LLOQ at 12 weeks post-transplant) for patients who have HCV RNA <LLOQ at their last HCV RNA measurement prior to transplant.
Patient disposition	Results presented represent an interim analysis. Of the 61 patients enrolled: 44 patients have had liver transplantation (41 with HCV RNA <LLOQ at transplant and 3 with HCV RNA>LLOQ at transplant); 10 discontinued pre-transplant treatment; 2 experienced HCC progression; 1 patient remains on treatment; 4 are post-treatment but waiting transplant.
Patient demographics and baseline characteristics	Enrolled patients had the following characteristics: median age 59 years; 80% male; 90% white; 67% with HCV RNA >6$\log_{10}$ IU/mL; 74% GT1; 13% GT2; 12% GT3a; 2% GT4; 78% non-CC IL28B genotype and 75% with prior HCV treatment experience. Baseline Child-Pugh-Turcotte liver disease scores were 5, 6, 7, and 8 in 43%, 30%, 23%, and 5% of patients. Median Model for End Stage Liver Disease score was 8.
Efficacy results	After initiation of treatment with SOF + RBV, HCV RNA was rapidly suppressed. At the time of transplant 41 of 44 patients had HCV RNA <LLOQ. Of those transplantees who had received ≥12 weeks of SOF treatment, 30 of 33 had HCV RNA <LLOQ. Of the 41 patients achieving virologic response at transplant, pTVR 12

Study P7977-2025 Pre-liver transplant	
	weeks after transplant was achieved in 64% of patients (25/39; 1 patient has not reached pTVR12 yet; 1 patient was lost to follow up at Week 8 post-transplant). There was no recurrence in 24/25 (96%) of patients who maintained HCV RNA target not detected >4 weeks prior to transplant. Duration of continuous viral suppression prior to transplant was the most predictive factor for pTVR in those who were HCV RNA <LLOQ at the time of transplantation.
Conclusion	For liver transplant patients all oral SOF + RBV for ≤ 48 weeks prior to transplantation prevented HCV recurrence in the majority of patients with 64% achieving post-transplant virological response compared with to a near universal historical risk of reinfection in the absence of prophylaxis. On treatment HCV RNA suppression in patients with well-compensated cirrhosis awaiting transplantation for HCC was rapid and similar to other patient populations on treated with sofosbuvir regimens. SOF + RBV offers the first all-oral regimen for use across all genotypes of patients awaiting liver transplantation.

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

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).**

Not applicable

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.

Not applicable

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.

6.7 *Indirect and mixed treatment comparisons*

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. 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 10.4, appendix 4.

Not applicable.

The sofosbuvir Phase 3 trials described in Sections 6.3 to 6.5 and 6.9 provide some direct evidence of comparative effectiveness versus comparators of relevance to current clinical practice – FISSION in HCV GT2/3 treatment-naïve patients. However, a mixed treatment comparison (MTC) was undertaken to explore the feasibility of obtaining comparative data for sofosbuvir versus all relevant comparators, across different HCV genotypes and other patient characteristics of relevance to the licensed indication for sofosbuvir.

A systematic review was conducted to assess the feasibility of deriving comparative efficacy data (SVR rates) for use in the economic model through a MTC.

For the purposes of populating the model the MTC was limited in two key areas:

- Due to the absence of data a MTC network could not be formed for all the populations of interest (i.e. GT2/3 treatment-experienced, GT4/5/6 treatment-naïve and IFN unsuitable patients).
- For patient groups where an MTC was feasible (treatment-naïve IFN eligible patients with GT1, GT2 or GT3 infection), these analyses had several limitations.
  - The structure of the health economics model required that efficacy data were split out by cirrhotic and non-cirrhotic status. In particular it was not possible to carry out meta-regressions and subgroup analyses distinguishing between GT2 and 3 and cirrhotic status simultaneously. It was also only feasible to run these analyses on a very small network thus rendering non-robust results.
  - In GT1 patients, a network including sofosbuvir was only possible by linking two small Phase 2 trials (ATOMIC and PROTON) which included only non-cirrhotic patients. In addition assumptions had to be made to be able to link the two phase II trials. Since sofosbuvir phase II trials included only non-cirrhotic patients these data has to be combined with the rest of the literature where the reported results were based on a combination of cirrhotic and non-cirrhotic patients. For this reason, the meta-regression carried out to provide separate results based on the cirrhotic status patients excluded sofosbuvir. A meta-regression was attempted to derive estimates for non-cirrhotic and cirrhotic patients. However, the network on which this analysis was based could not include sofosbuvir, limiting the utility of the GT1 MTC results as inputs for the cost-effectiveness model.

- In GT2 and GT3 patients the MTC results were based on those obtained for non-cirrhotic and cirrhotic patients combined (i.e. no separate cirrhotic or non-cirrhotic data available) as the split by both GT (GT2 and 3 respectively) and cirrhotic status was not available in the literature. A meta-regression was subsequently conducted to obtain the results for non-cirrhotic and cirrhotic patients separately. However, the results from the meta-regression were for GT2 and 3 combined. To obtain the results for non-cirrhotic and cirrhotic patients split by genotype the following assumptions had to be made: 1) That the meta-analysis results for GT2 and GT3 combined patients were considered for non-cirrhotic patients; 2) The odds ratio between non-cirrhotic and cirrhotic, obtained from the meta-regression for GT2 and 3 combined, was applied to the previous MTC results to obtain the results for cirrhotic patients. Therefore any results obtained are to be used with caution given the fact that the results two meta-analyses had to be combined to estimate them.
- One major limitation of using the results of the MTC for GT3 is that the treatment regimen included in the network (12 weeks of SOF + RBV) is no longer the licensed regimen for this indication (i.e. SOF+PEG-IFN+RBV for 12 weeks or SOF+RBV for 24 weeks).

As such, the results from the MTC could not be considered robust and it was considered most appropriate to populate the economic base case with efficacy data from individual studies in all patient groups.

In order to provide the ERG and NICE with information of the MTC further details are provided in Appendix 4.0.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Not applicable.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Not applicable.

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

Not applicable.

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Not applicable.

6.7.6 Please present the results of the analysis.

Not applicable.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Not applicable.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

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

6.9 *Adverse events*

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

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 3 trials were designed to primarily assess clinical efficacy and hence a full systematic review has not been undertaken. In each study assessment of safety was a secondary objective and the results are reported here.

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. A suggested format is shown below.

6.9.2.1 Treatment naïve patients – NEUTRINO and FISSION

HCV GT1, 4, 5 or 6 Treatment naïve - NEUTRINO

Details of discontinuation of treatment, adverse events, and haematologic abnormalities are provided in Table 32.

The mean duration of treatment with SOF + PEG-IFN-2a + RBV was 12 weeks (SD, 1 week). During this time, only 5 patients (2%) discontinued treatment due to adverse events. Serious adverse events occurred in 4 patients (1%). The most common adverse events were fatigue (59%), headache (36%), nausea (34%), and insomnia (25%). (Table 32)

Table 32: NEUTRINO - Discontinuation of Treatment, Adverse Events, and Haematologic Abnormalities (Lawitz et al. 2013a)[17]

Event	SOF+PEG-IFN-2a+RBV for 12 Weeks N=327
Mean duration of treatment, weeks	12±1
Treatment discontinuation due to an adverse event, n (%)	5 (2)
Serious adverse event during treatment, n (%)	4 (1)
Any adverse event during treatment, n (%)	310 (95)
Grade 3/4 adverse events, n (%)	48 (15)
Common adverse events, n (%)*	
Fatigue	192 (59)
Headache	118 (36)
Nausea	112 (34)
Insomnia	81 (25)
Anaemia	68 (21)
Rash	59 (18)
Decreased appetite	58 (18)
Pyrexia	58 (18)
Neutropenia	54 (17)
Pruritus	54 (17)
Chills	54 (17)
Influenza-like illness	51 (16)
Myalgia	45 (14)
Irritability	42 (13)
Diarrhoea	38 (12)
Haematologic events, n (%)	
Haemoglobin level < 10 g/dL	74 (23)
Haemoglobin level < 8.5 g/dL	8 (2)
Lymphocyte count 350-500/mm^3	17 (5)
Lymphocyte count < 350/mm^3	0
Absolute neutrophil count 500-750/mm^3	49 (15)
Absolute neutrophil count < 500/mm^3	17 (5)
Platelet count < 50,000/mm^3	1 (< 1)
White cell count 1,000-1,500/mm^3	18 (6)
White cell count < 1,000/mm^3	0

PEG-IFN-2a, peglylated interferon alpha 2a; RBV, ribavirin; SOF, sofosbuvir

*Events reported in at least 15% of patients

HCV GT 2 or 3 -Treatment naïve - FISSION

The FISSION trial was designed to evaluate the efficacy and safety of SOF + RBV versus PEG-IFN-2a + RBV in patients with HCV genotype 2 or 3 who had not received any previous treatment for HCV infection. Safety was a secondary endpoint.

Details of discontinuation of treatment, adverse events, and haematologic abnormalities are provided in Table 33.

The mean treatment duration with SOF + RBV was 12 weeks (SD, 2 weeks) and 21 weeks (SD, 6 weeks) with PEG-IFN-2a + RBV. Adverse events occurred in fewer patients in the SOF + RBV group compared with the PEG+RBV group (86% vs. 96%). Only 3 patients (1%) discontinued SOF + RBV because of adverse events compared with 26 patients (11%) receiving PEG-IFN-2a + RBV. The rates of serious adverse events were low in both treatment groups and Grade 3 or 4 adverse events were reported in fewer patients in the SOF+RBV group (7%) versus the PEG-IFN-2a + RBV group (18.5%).

The safety profile of SOF + RBV was similar to the expected safety profile of ribavirin; treatment with sofosbuvir did not result in any additional or unique safety signals.

The most common adverse events in either treatment group were fatigue, headache, nausea, and insomnia. All adverse events occurring in at least 10% of patients occurred more frequently in the PEG-IFN-2a + RBV group than in the SOF + RBV group.

The characteristics side effects of influenza-like symptom and fever associated with interferon therapy were reported in 11 and 14% of patients receiving PEG-IFN-2a + RBV but in only 2 and 3% of patients receiving SOF + RBV. Depression, another common side effect of interferon therapy, occurred in 14% of patients receiving PEG-IFN-2a + RBV compared with 5% of patients receiving SOF + RBV.

Haematological adverse events were more common among patients in the PEG-IFN-2a + RBV compared with the SOF + RBV group. Decreases in haemoglobin to less than 10 mg/dL and less than 8.5 mg/dL were 9% and 1% with SOF + RBV compared with 14% and 2% with PEG-IFN-2a + RBV. Rates of decreased lymphocyte, platelet, and white-cell counts ranged from 1% to 7% among patients receiving PEG-IFN-2a + RBV, whereas no patients receiving SOF + RBV had decreases in these measures.

Table 33: FISSION - Discontinuation of Treatment, Adverse Events, and Haematologic Abnormalities(Lawitz et al. 2013a and CSR)[17;74]

Event	SOF+RBV for 12 Weeks N=256	PEG-IFN-2a+RBV for 24 Weeks N=243
Mean duration of treatment (weeks)	12±2	21±6
Treatment discontinuation due to an adverse event — n (%)	3 (1)	26 (11)
Serious adverse event during treatment — n (%)	7 (3)	3 (1)
Any adverse event during treatment — n (%)	220 (86)	233 (96)
Grade 3 or 4 adverse events	18 (7)	45 (18.5)
Common adverse events, n (%)*		
Fatigue	92 (36)	134 (55)
Headache	64 (25)	108 (44)
Nausea	46 (18)	70 (29)
Insomnia	31 (12)	70 (29)
Irritability	25 (10)	40 (16)
Rash	23 (9)	43 (18)
Diarrhoea	23 (9)	42 (17)
Anaemia	20 (8)	28 (12)
Myalgia	21 (8)	40 (16)
Pruritus	19 (7)	42 (17)
Decreased appetite	17 (7)	44 (18)
Influenza-like illness	7 (3)	44 (18)
Chills	7 (3)	43 (18)
Pyrexia	6 (2)	33 (14)
Neutropenia	0	30 (12)
Hematologic events, n (%)		
Haemoglobin level < 10 g/dL	23 (9)	35 (14)
Haemoglobin level < 8.5 g/dL	1 (< 1)	4 (2)
Lymphocyte count 350 to 500/mm^3	0	15 (6)
Lymphocyte count < 350/mm^3	0	12 (5)
Absolute neutrophil count 500 to 750/mm^3	0	30 (12)
Absolute neutrophil count < 500/mm^3	0	6 (2)
Platelet count < 50,000/mm^3	0	18 (7)
White-cell count 1,000 to 1,500/mm^3	0	10 (4)
White-cell count < 1,000/mm^3	0	1 (< 1)

PEG-IFN-2a, peglylated interferon alpha 2a; RBV, ribavirin; SOF, sofosbuvir

* Reported in at least 15% of patients in any study group

6.9.2.2 Treatment experienced HCV GT2 or 3 - FUSION

Details of discontinuation of treatment, adverse events, and haematologic abnormalities are provided in Table 34.

The mean duration of treatment with SOF + RBV was 12 weeks (SD, 0.6 weeks) in the 12-week treatment group and 16 weeks (SD, 0.2 weeks) in the 16-week treatment group. During the treatment phase only 1 patient discontinued treatment and this was during the placebo period in the 12-week group.

The most common adverse events were fatigue, headache, nausea, and insomnia.

There were no notable differences in adverse event or laboratory abnormality frequencies between the 12-week and the 16-week groups.

Table 34: FUSION - Treatment discontinuation, adverse events and haematologic abnormalities (Jacobson et al. 2013a)[17]

Event	SOF+Ribavirin for 12 Weeks	SOF+Ribavirin for 16 Weeks
Mean duration of treatment, weeks (SD)	12 (0.6)	16 (0.12)
Any adverse events, n (%)	92 (89)	86 (88)
Grade 3-4 adverse events, n (%)	8 (8)	4 (4)
Serious adverse events, n (%)	5 (5)	3 (3)
Treatment discontinuations due to adverse events, n (%)	1 (1)	0
Common adverse events, n (%)*		
Fatigue	46 (45)	46 (47)
Headache	26 (25)	32 (33)
Insomnia	21 (20)	28 (29)
Nausea	22 (21)	20 (20)
Irritability	15 (15)	11 (11)
Cough	10 (10)	13 (13)
Diarrhoea	15 (15)	6 (6)
Arthralgia	11 (11)	9 (9)
Pruritus	12 (12)	7 (7)
Rash	7 (7)	12 (12)
Anaemia	11 (11)	4 (4)
Haematologic abnormalities		
Haemoglobin < 10 g/dL, n (%)	10 (10)	5 (5)
Haemoglobin < 8.5 g/dL, n (%)	2 (2)	0
Absolute neutrophil count < 750/mm^3, n (%)	1 (1)	0
Platelets < 50,000/mm^3, n (%)	2 (2)	0
White cell count 1000 to 1500 per mm^3	0	0
White cell count <1000 per mm^3	1(1)	0

RBV, ribavirin; SOF, sofosbuvir

* Reported in at least 10% of patients

6.9.2.3 Treatment-naïve and experienced, IFN unsuitable HCV GT2 or 3 - POSITRON

Details of discontinuation of treatment, adverse events, and haematologic abnormalities are provided in Table 35.

The mean treatment duration was similar for the SOF + RBV and placebo groups with mean (SD) exposures of 11.9 weeks (1.33 weeks) and 11.8 weeks (1.60 weeks), respectively. Four patients (2%) who received SOF + RBV discontinued treatment due to adverse events compared with 3 patients (4%) in the placebo group. The safety profile of SOF + RBV was consistent with the known safety profile of RBV.

The most marked differences in reported adverse events between the SOF + RBV and placebo groups were those that had previously been observed with RBV treatment, including fatigue, insomnia, anaemia and dyspnea.

Table 35 POSITRON: Treatment discontinuation, adverse events and haematologic abnormalities (Jacobson et al. 2013a)[18]

Event	SOF+RBV for 12 Weeks N=207	Placebo N=71
Mean duration of treatment	12±1.3	12±1.6
Treatment discontinuations due to adverse events, n (%)	4 (2)	3 (4)
Serious adverse events, n (%)	11 (5)	2 (3)
Any adverse events, n (%)	185 (89)	55 (78)
Common adverse events*		
Fatigue	91 (44)	17 (24)
Nausea	46 (22)	13 (18)
Headache	43 (21)	14 (20)
Insomnia	39 (19)	3 (4)
Anemia	27 (13)	0
Pruritus	23 (11)	6 (8)
Irritability	19 (9)	1 (1)
Diarrhoea	19 (9)	4 (6)
Rash	18 (9)	6 (8)
Arthralgia	16 (8)	1 (1)
Cough	11 (5)	2 (3)
Haematologic abnormalities		
Haemoglobin < 10 g/dL, n (%)	15 (7)	0
Haemoglobin < 8.5 g/dL, n (%)	2 (1)	0
Absolute neutrophil count < 750/mm^3, n (%)	0	1 (1)
Platelets < 50,000/mm^3, n (%)	0	2 (3)

Ribavirin; RBV, ribavirin; SOF, sofosbuvir

*****Reported in at least 10% of patients in any group

6.9.2.4 Treatment naïve and treatment experienced HCV GT 2 or 3 - VALENCE

Details of discontinuation of treatment, adverse events, and haematologic abnormalities are provided in Table 36.

Adverse events generally occurred more commonly with active treatment compared with placebo, with the exception of headache, fatigue, and nasopharyngitis which were reported with similar frequencies in placebo and active treatment groups. The incidence of pruritus, asthenia, insomnia, dry skin, dyspnea, and cough were similar in the SOF + RBV 12 Week and SOF + RBV 24 Week treatment groups. Diarrhoea and irritability were approximately twice as frequent in the SOF + RBV 24 week treatment group compared with the SOF + RBV 12 Week treatment group. Nausea was more commonly reported with SOF + RBV for 12 weeks (31.0%) compared with either placebo treatment (10.6%) or SOF + RBV 24 weeks (12.8%). Most of the reported laboratory abnormalities were Grade 1 or 3 in severity. Grade 3 abnormalities were more common with SOF + RBV for 12 or 24 weeks.

Table 36: VALENCE: Treatment discontinuation, adverse events and haematologic abnormalities (Interim CSR)[19]

Event	GT2/3 Placebo n=85	GT2/3 SOF+RBV 12 weeks N=84	GT3 SOF+RBV 24 weeks n=250
Number (%) of subjects experiencing			
Treatment discontinuation due to an adverse event — n (%)	XXXXXX	XXXXXX	XXXXXX
Serious adverse event during treatment — n (%)	XXXXXX	X	XXXXXX
Any adverse event during treatment — n (%)	XXXXXX	XXXXXX	XXXXXX
Grade 3 or 4 adverse events	XXXXXX	XXXXXX	XXXXXX
Common adverse events, n (%)*			
Fatigue	XXXXXX	XXXXXX	XXXXXX
Headache	XXXXXX	XXXXXX	XXXXXX
Nausea	XXXXXX	XXXXXX	XXXXXX
Insomnia	XXXXXX	XXXXXX	XXXXXX
Irritability	XXXXXX	XXXXXX	XXXXXX
Diarrhoea	XXXXXX	XXXXXX	XXXXXX
Pruritus	XXXXXX	XXXXXX	XXXXXX
Asthenia	XXXXXX	XXXXXX	XXXXXX
Nasopharyngitis	XXXXXX	XXXXXX	XXXXXX
Dry skin	XXXXXX	XXXXXX	XXXXXX
Dyspnoea	XXXXXX	XXXXXX	XXXXXX
Cough	XXXXXX	XXXXXX	XXXXXX
Grade 3 and 4 laboratory abnormalities			
Haemoglobin	XX	XX	XXX
Grade 3	XXXXXX	XXX	XXXXXX
Lymphocytes	XX	XX	XXX
Grade 3	X	XXXXX	XXXXXX
Neutrophils	XX	XX	XXX
Grade 3	XXXXXX	XXXXXX	X
Platelets	XX	XX	XXX
Grade 3	X	X	XXXXXX

Ribavirin; RBV, ribavirin; SOF, sofosbuvir
*****Reported in at least 10% of patients

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

The safety and tolerability data from the Phase 3 studies demonstrate that sofosbuvir is well tolerated and has a side effect profile which is similar to placebo and significantly superior to the current standard of care. In clinical practice this has the potential to reduce the level of resource utilization, free up service capacity within HCV treatment, allow for more patients to become willing to be actively treated and improve patients treatment experience compared with current standard of care.

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.

The efficacy and safety of sofosbuvir for the treatment of chronic hepatitis in adults has been assessed in a comprehensive clinical trial programme, comprising five pivotal randomised, multi-centre Phase 3 studies (NEUTRINO, FISSION, FUSION, POSITRON and VALENCE), and a large number of supporting Phase 2 studies and

studies in special populations. This comprehensive evidence base supports the licensed use of sofosbuvir-based regimens across all HCV genotypes (GT1–6). In addition, the evidence supports the use of sofosbuvir in both treatment-naïve patients and also 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 or those awaiting liver transplant.

Across Phase 3 and Phase 2 clinical studies, treatment with sofosbuvir-based regimens resulted in a rapid, profound and sustained decline in HCV RNA levels, with the majority of patients achieving a rapid virologic response below the level of quantification after 4 weeks of treatment, across all genotypes. This on-treatment response negates the need for on-treatment monitoring of HCV RNA or response-guided therapy for sofosbuvir-based regimens, in contrast to other therapies.

Sofosbuvir also has high barrier to the development of treatment-resistant mutations. No drug resistance or drug-associated virological breakthrough was observed in the Phase 3 studies. This means that sofosbuvir can be re-used (in combination with other products) if required.

Benefits for the specific genotypes groups are as follows:

<u>HCV GT1, 4, 5 or 6</u>

- Improved efficacy (superior efficacy vs. current standard of care) with a shorter treatment duration (12 weeks compared with 48 weeks).
- In the full study population of the phase 3 study NEUTRINO (GT1, 4, 5, 6; n=327), the SVR12 rate for the sofosbuvir regimen (90% [91% revised analysis]) was significantly better ($p<0.001$) than a FDA-approved historical control rate of 60% based on the pivotal telaprevir (ADVANCE) and boceprevir (SPRINT-2) clinical trials.
- NEUTRINO included substantial proportions of patients with baseline characteristics that have historically been associated with lower rates of response to treatment, including cirrhosis, high baseline viral load, low platelet counts, high BMI, black race and a non-CC IL28B genotype; high SVR12 rates (≥ 80%; analysis for all genotypes) were also achieved in these more difficult-to-treat patients.

<u>HCV GT1 treatment-naïve patients</u>

- In the pivotal phase 3 study NEUTRINO SOF + PEG-IFN-2a + RBV for 12 weeks resulted in high rates of sustained virologic response 12 weeks after the end of treatment (SVR12) in GT1 patients (sub-group analysis: 262/292 patients; 90%).
- The 81% SVR12 rate achieved in GT1 patients with compensated cirrhosis is the highest rate ever reported with any currently approved treatment regimen in this challenging sub-population.

<u>HCV GT1 treatment experienced patients</u>

- Sofosbuvir in combination with peginterferon+ribavirin was not studied in a Phase 3 study in HCV GT1 treatment-experienced patients in the first wave of the sofosbuvir development program.
- During the FDA's Advisory Committee meeting on the 25th October 2013, the FDA asked whether the high SVR rate in GT1 treatment-naïve population (approximately 90%) provided enough evidence to support use of SOF + PEG-IFN + RBV for treatment of CHC in GT1 patients who previously failed to respond to a course of peginteferon and ribavirin.

- Historically, approximately 50% of treatment-naïve GT1 patients have responded to peginterferon+ribavirin treatment with 50% failing to respond. In NEUTRINO, 91% of treatment-naïve GT1 patients responded to the combination of SOF + PEG-IFN-2a + RBV. The higher rate of overall SVR observed in NEUTRINO is likely driven by successful treatment of a proportion of patients who would likely be PEG-IFN + RBV failures (with the assumption that all patients that would have achieved SVR with PEG-IFN+RBV achieved an SVR with SOF+ PEG-IFN+RBV). The increase in SVR (from 50 to 91%) is representative of the efficacy of SOF + PEG-IFN + RBV in the 50% non-responders that historically would be expected to be in the study. The FDA therefore concluded that given the high SVR rates in NEUTRINO, 39/50 (78%) of peginterferon+ribavirin non-responders are likely to respond to SOF + PEG-IFN + RBV treatment, yielding the approximate SVR rate of 78% in the GT1 PEG+RBV treatment naive population.

<u>HCV GT2 treatment-naïve and treatment experienced patients</u>

- In treatment-naïve GT2 patients SOF + RBV for 12 weeks was significantly better than standard of care PEG-IFN-2a + RBV for 24 weeks in achieving SVR12 (FISSION Phase 3 sub-group analysis: 97% vs. 78%; between treatment difference, 19.5%, 95% CI 8.4%, 31.5%). Response rate in GT2 cirrhotic patients was also high for sofosbuvir (SVR12, 91%).
- In treatment-experienced GT2 patients (FUSION Phase 3; failed on previous IFN therapy) and GT2 patients who are unsuitable for IFN therapy (POSITRON, Phase 3), SVR12 rates with SOF + RBV for 12 weeks were 86% and 93%, respectively (sub-group analyses). SOF + RBV for 12 weeks provides a simple, all-oral (IFN-free) regimen in these patient groups which currently have limited or no treatment options.

<u>HCV GT3 treatment-naïve and treatment experienced patients</u>

- Historically patients with GT2 and GT3 infection have been grouped together as 'easier-to-treat' genotypes compared with others such as GT1. The pivotal Phase 3 sofosbuvir studies, FISSION, FUSION and POSITRON, took the same approach and studied SOF + RBV for 12 weeks in patients with HCV GT2/3 infection. The results demonstrated that GT3 is harder to treat than GT2 and are consistent with growing expert opinion that GT2 and GT3 HCV behave differently and should be considered separately in terms of treatment approach and how to be studies in future trials.
- The sofosbuvir licence considers GT3 as a distinct population and recommends 12 weeks of triple therapy with SOF + PEG-IFN + RBV or 24 weeks of treatment with SOF + RBV. Evidence supporting these regimens in GT3 patients is drawn from the Phase 3 study VALENCE, as well as additional data from small Phase 2 studies (ELECTRON and PROTON), demonstrating high SVR12 rates in treatment-naïve and experienced patients.
- SOF + PEG-INF+RBV for 12 weeks:
  - In treatment-naïve patients, sofosbuvir triple therapy resulted in SVR12 rates of 90% (PROTON, Phase 2) and 100% (ELECTRON, Phase 2). However patient numbers were small (GT3 patients: n=10 and 29, respectively).[†]
  - In treatment-experienced GT3 patients, 12 weeks of sofosbuvir triple therapy (LONESTAR-2) resulted in SVR12 rate of 83% (sub-group analysis, n=24).
- SOF + RBV for 24 weeks:

  In VALENCE (Phase 3) an SVR12 rate of 93% was achieved with SOF + RBV for 24 weeks in treatment-naïve GT3 patients (sub-group analysis). In treatment-experienced GT3 patients the same regimen resulted in an SVR12 rate of 77%

(sub-group analysis). These populations included patients that were unsuitable for IFN, a population for which there are no treatment options.

HCV GT4, GT5 or GT6 patients

- Sofosbuvir (in combination with PEG-IFN + RBV for 12 weeks) is the only direct acting HCV antiviral agent to have been studied in these genotypes in Phase 3 trials to date and has resulted in high rates of SVR12 in GT4/5/6 patients. Although patient numbers, particularly for GT5 and GT6, are limited, this reflects the limited number of patients in the 'under treater care' population with these HCV genotypes (NEUTRINO Phase 3 sub-group analysis: 34/35 patients; 97%).

QoL

- Health-related quality of life (HRQoL) following 12 weeks SOF + RBV treatment is similar to that reported for placebo-treated HCV patients (POSITRON). From baseline through to the end of treatment there is less HRQoL impairment with this all-oral treatment regimen than with PEG + RBV (FISSION).

HIV co-infected patients

- SVR12 rates observed in patients with HCV/HIV co-infection are similar to those seen in HCV mono-infected patients (PHOTON-1, Phase 3). In treatment-naïve patients; 76% in GT1 (SOF + RBV 24 weeks), 88% in GT2 and 67% in GT3 (both SOF+RBV 12 weeks) and in treatment-experienced patients; 93% in GT2 and 92% in GT3 (SOF + RBV 24 weeks).

HCV patients - pre liver transplantation

- In patients who are HCV RNA-positive at the time of liver transplant, reinfection is universal and can lead to accelerated progression to cirrhosis, graft failure and death (Gane 2008)[80]. Treatment with SOF + RBV prior to transplant prevented HCV recurrence in 64% (25/39) of patients and there was no recurrence in 24/25 (96%) of patients who maintained HCV RNA target not detected for >4 weeks prior to transplant (Study P7977-2025 Phase 2).

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

Strengths

- The efficacy and safety of sofosbuvir for the treatment of CHC in adults has been assessed in a comprehensive clinical trial programme, comprising of:
    - Five pivotal randomised, multi-centre Phase 3 studies (NEUTRINO, FISSION, FUSION, POSITRON and VALENCE) across all genotypes
    - A large number of supporting Phase 2 studies
    - Studies in special populations including HIV co-infected patients and pre-liver transplant patients.

  This comprehensive evidence base supports the licensed use of sofosbuvir-based regimens across all HCV genotypes (GT1–6). In addition, the evidence supports the use of sofosbuvir in treatment-naïve patients, and also 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 awaiting liver transplant.

- The Phase 3 studies were, multicentre studies with recognised clinically valid endpoints. The Phase 3 studies (NEUTRINO, FISSION, POSITRON and FUSION) have been published in the New England Journal of Medicine.

- A wide range of patients groups have been studied including those who are normally deemed more difficult to treat (such a patients with a high BMI and those with cirrhosis) and patients con-infected with HIV. It is important to note that the phase III trials included the largest number of cirrhotic patients enrolled to date in HCV direct-acting antiviral clinical trials. The clinical trial population is reflective of the patient population in clinical practice that will be eligible to receive sofosbuvir.

- Study populations in these trials included substantial proportions of patients with characteristics that have historically been associated with lower rates of response to treatment including cirrhosis a high baseline viral load, black race and a non-CCIL28B GT.

- No on treatment virological breakthrough was observed and relapse without resistance accounted for all virological failures in the phase III trials except for one patient who experienced viral breakthrough associated with non adherence.

- Studies are relevant to the final NICE scope and the licensed indication for sofosbuvir.

<u>Limitations</u>

- No UK specific Phase 3 studies have been performed however trials have been conducted in populations that can be considered as broadly representative of the UK population; NEUTRINO, FISSION, FUSION, POSITRON and VALENCE were conducted across the USA, Canada, Australia, New Zealand and Europe.

- ***GT1/4/5/6***

    - NEUTRINO was a single-arm open-label study which provides pivotal evidence to support the use of sofosbuvir in combination with PEG-IFN and RBV in treatment-naïve patients with GT1/4/5/6 infection. The single-arm/open-label design and the lack of a direct head-to-head comparison with the current standard of care in GT1 infection (the protease inhibitors boceprevir and telaprevir) could be considered as a limitation, though it was agreed as an approach with the regulatory authorities

    - However, the study was designed to test the hypothesis that rates of sustained virologic response 12 weeks after treatment cessation (SVR12) for sofosbuvir-treated patients would be superior to an historical control, based on previously reported data for boceprevir and telaprevir in a trial population of cirrhotic and non-cirrhotic patients. The trial resulted in an SVR12 rate of 90% for sofosbuvir that was significantly higher than the historic control rate of 60% ($p<0.001$). This approach was agreed with the regulatory authorities (FDA), owing to the "expectation of high response rates, improved safety, and shorter treatment duration" with sofosbuvir.

    - The standard of care in GT4/5/6 is currently PEG-IFN+RBV for 48 weeks. Given the mixed genotypic population in this trial (GT1/4/5/6), the standard of care in GT1 being boceprevir and telaprevir, and GT1 being the predominant genotype in this study population and in clinical practice, it would have been unethical to consider PEG-IFN+RBV as a suitable

comparator across all the genotypes included in this study. In addition, long-term treatment with PEG-IFN+RBV can be associated with severe fatigue, depression, skin reactions and haematological events, including anaemia, thrombocytopenia and neutropenia and tolerability in clinical practice.

- In relation to the open-label design, blinding of NEUTRINO was deemed to be too complex given the different durations of treatment for SOF + PEG-IFN + RBV versus the possible comparators of protease inhibitor triple therapy or PEG-IFN + RBV (12 weeks versus up to 48 weeks, respectively).

- The safety profile in the Phase 2 studies of SOF + PEG-IFN + RBV demonstrated no significant added toxicity to the events expected with PEG-IFN + RBV and low discontinuation rates with a short duration of therapy. This contrasted with the less favourable safety profile of a protease inhibitor when added to PEG-IFN + RBV.

- In the absence of a protease inhibitor-based regimen, broader inclusion criteria could be employed. Specifically, concomitant medication restrictions were minimal - opiate substitution therapy with methadone or buprenorphine was permitted, as were CYP3A4 inhibitors and inducers. Furthermore, a high percentage of cirrhotic patients were targeted for enrolment.

- Although NEUTRINO included patients with GT1, 4, 5 and 6, the numbers of patients with either GT5 or GT6 infection were very limited. However, the number of patients included in the trial does reflect UK clinical practice — and is in line with the numbers studied for other licensed treatments.

- Sofosbuvir has not been studied in a Phase 3 trial in treatment-experienced patients with GT1, 4, 5 and 6 HCV infections. As such the optimal treatment duration in this population has not been established. However, as per the SmPC and per Regulatory Authority direction, consideration should be given to treating these patients, and potentially extending the duration of therapy with SOF + PEG-IFN+RBV beyond 12 weeks and up to 24 weeks. It should be noted that given the high level of unmet need in this population both the FDA and EMA considered a model which extrapolated SVRs from existing sofosbuvir data.

- GT2/3

  - HCV GT2 and GT3 treatment-naïve patients have historically been considered to have a more favourable response to treatment with PEG-IFN+RBV than other genotypes. Multiple studies have shown that SVR occurs in approximately 40-50% of patients with HCV GT1 who receive 48 weeks of dual therapy with PEG-IFN + RBV (EASL 2014)[13], whereas considerably higher SVR rates are achieved in patients with GT2/3 infection with only 24 weeks of PEG-IFN + RBV therapy (EASL 2014)[13]. As a result, GT2 and GT3 have historically been grouped together in clinical trials involving PEG + RBV, and the pivotal Phase 3 sofosbuvir studies – FISSION, FUSION and POSITRON – took the same approach. However, sub-group results from these three studies showed that SVR12 rates were much lower for GT3 infection when using the same sofosbuvir regimen and treatment duration (SOF + RBV 12 weeks). This trend was

also observed in the PEG + RBV comparator arm of FISSION (78% in GT2 and 63% in GT3). These results are consistent with the growing expert opinion that GT2 and 3 HCV behave differently and should be studied and considered separately. Accordingly, the licence for sofosbuvir considers GT3 as a distinct population and recommends triple therapy of PEG-IFN + RBV for 12 weeks or a longer duration of treatment with SOF + RBV (24 weeks). Evidence supporting these regimens in GT3 patients is drawn from the Phase 3 study VALENCE, as well as additional data from Phase 2 studies, demonstrating high SVR12 rates in these patients.

  - POSITRON evaluated GT2 and GT3 patients who had previously discontinued IFN therapy owing to unacceptable adverse events, who had a concurrent medical condition precluding therapy with an IFN-containing regimen, or who had decided against treatment with an IFN-containing regimen. The POSITRON trial included a blinded placebo arm, rather than a standard of care active comparator, as there is no current standard of care for these patients.

- Pre -transplant populations

  - Evidence in pre-transplant patients comes from a single arm, open-label study which could be considered a limitation however as this is no current standard of care for this patient group and therefore an appropriate comparator is not available the approach taken is valid and relevant.

6.10.3 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.

A wide population has been studied including patients from the UK and the studies reflect the broad patient population in the real world who will be eligible for treatment. The efficacy outcomes seen within the clinical trials are therefore expected in real-life clinical practice.

The primary outcome SVR12 is appropriate and accepted in the clinical and regulatory environment. The EASL guideline states that the primary goal of therapy is to eradicate the HCV infection with SVR acting as the indicator for this representing a cure (EASL 2014)[13]. 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 (Ng *et al*. 2011, van der Meer *et al*. 2012)[10;11].

Through improving cure rates together with increasing the number of patients eligible for treatment sofosbuvir has 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. It should be noted that the EMA accepted an accelerated regulatory process for sofosbuvir, a designation only granted to those medicines of major public health interest.

6.10.4 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 SmPC?

There are no factors anticipated that will influence the external validity of the results observed in the Phase 3 clinical trials to those expected in clinical practice. The dose used in the clinical trials reflects that which will be used in clinical practice. A wide population has been studied and the studies reflect the broad patient population in the real world who will be eligible for treatment.

In addition it should be noted that sub-group analyses have demonstrated that demographic factors including race and ethnic group, as well as age and sex, did not have a significant impact on the SVR12 rates achieved.

HCV genotype can influence the responsiveness of the disease to treatment and the distribution of HCV genotype can vary geographically. However, the applicability of evidence obtained across the entire clinical trial programme for sofosbuvir in relation to each genotype is not influenced by any such geographical disparities.

A wide range of patient groups have been studied in sofosbuvir trials including substantial proportions of patients with characteristics that have historically been associated with lower rates of response to treatment (Lawitz *et al* 2013a)[17] and that reflect patient characteristics seen in clinical practice. These include older age, BMI, cirrhosis, a high baseline HCV viral load, black race and a non-CC IL28B genotype. Sub-group analyses across NEUTRINO, FISSION, FUSION and POSITRON showed that SVR12 rates with sofosbuvir-based regimens were not significantly affected by any predefined patient characteristic other than cirrhosis and non-CC IL28B genotype

No patient selection criteria are required in clinical practice.

Within the phase III programme the full evidence base is for the given for the licensed dose.

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 review of the literature was performed to identify all published studies that had assessed the cost-effectiveness of treatments currently used for chronic HCV. The systematic searches were conducted using the following electronic databases:

- *PubMed*
- *EMBASE (Ovid)*; and
- *CRD (Centre for Review and Dissemination) databases* (i.e. *DARE (Database of Abstracts of Reviews of Effects)*, *HTA (Health Technology Assessment)*, *NHS-EED (NHS-Economic Evaluation Database*).

The search terms were defined based on the disease area, population (adult chronic HCV patients), outcomes of interest (e.g. costs, LYs gained, QALYs and ICERS) and relevant publication types (e.g. cost studies, HTAs and economic evaluations). Search terms for the outcomes of interest were defined broadly to obtain the maximum number of relevant articles.

Due to the breadth of literature and the changing nature of cost and cost-effectiveness over time, the search was limited to studies published in the last 10 years (i.e. 2002 to the literature search date in September 2012) in the original review. This search was further updated to include all studies published up to the literature search date in October 2013. All searches were designed to build on previous searches performed in systematic literature reviews by NICE and the Cochrane Collaboration. Detailed literature search strategies are provided in section Error! Reference source not found.. In addition, a manual search of the reference list from included systematic reviews published from 2010 onwards was conducted to ensure that no publications were overlooked.

Following the searches in the aforementioned databases, all potentially eligible references were imported into the Reference Manager software and any duplicates were removed. The titles and abstracts of the remaining references were reviewed by two independent reviewers based on the inclusion and exclusion criteria that were defined by the PICOS (Patient-Intervention-Comparator-Outcome-Study) methodology detailed in Table 37. In the instance of discrepancies between the two decisions, arbitration was carried out by an independent reviewer.

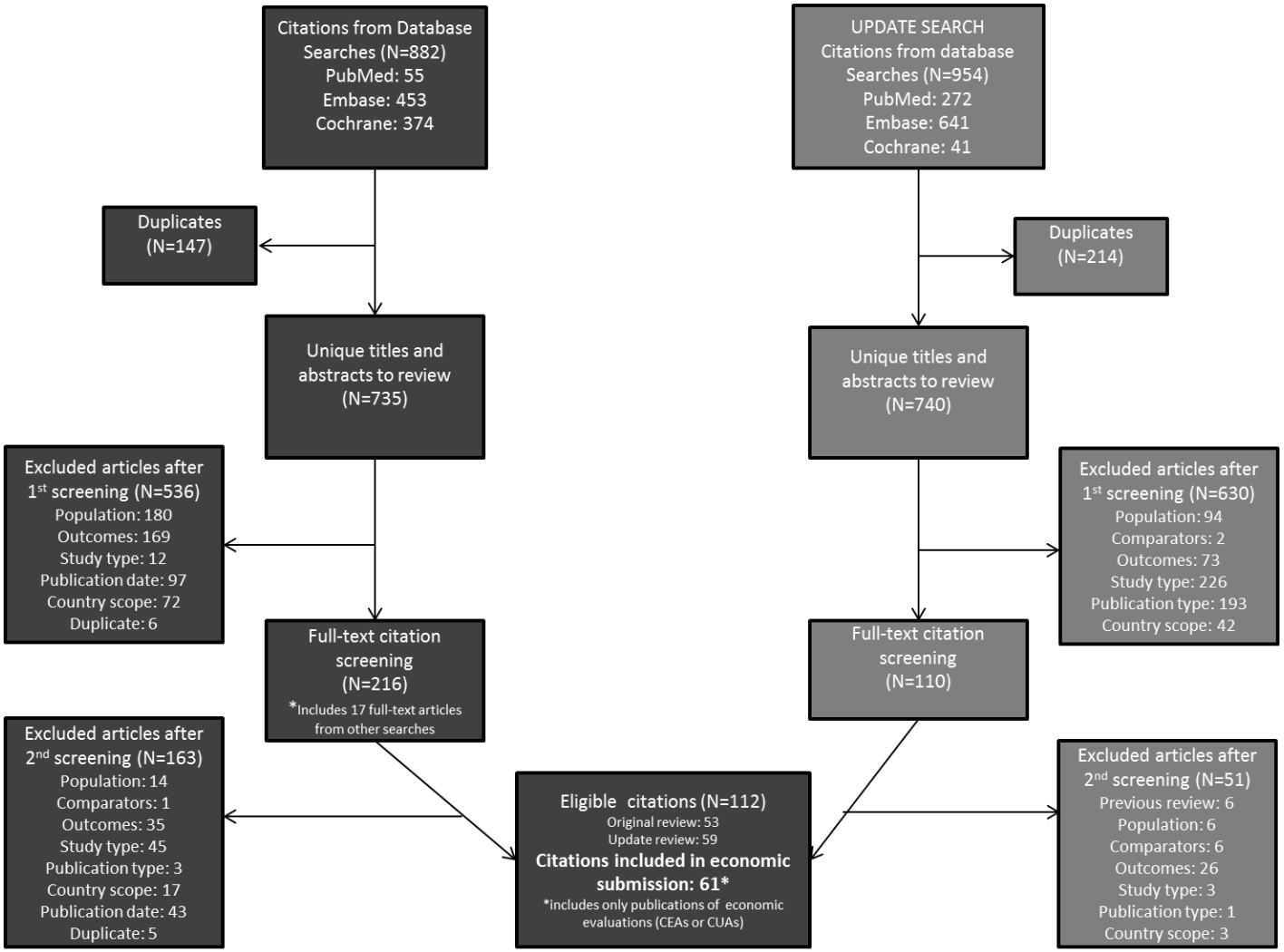
Table 37 Eligibility criteria for cost effectiveness studies

Category	Inclusion Criteria	Exclusion Criteria
Disease and population	• Infection with Hepatitis C virus (HCV), genotypes 1-6 • Adults (> 18 years) • TN patients • TE patients: relapsers, non-partial- and null-responders • HIV co-infected patients	• Studies in children • Economic studies on following disease and population: ▪ Not focussed on adult (> 18 years) ▪ Studies on smaller population (< 10) ▪ Acute HCV ▪ Recurrent HCV ▪ HCV/HBV co-infected ▪ Renal dysfunction ▪ Depression ▪ Studies focussing on homeless populations and intravenous drug users (IDU)
Interventions	• HCV screening programmes • HCV treatments (e.g., PEG-IFN, RBV, SOF, telaprevir, boceprevir) • Watchful waiting	• Studies not reporting impact on economic outcomes
Outcomes	• Costs • Resource use • QALYs • LYG • Productivity losses	• Non-economic outcomes ▪ Efficacy ▪ Safety ▪ QoL ▪ HCV sequence
Study type	• Economic evaluations • Health technology assessments • Systematic reviews	• Studies not reporting impact on economic outcomes
Language	• Studies in English, French, German, Spanish Italian	• All other languages besides English, French, German, Spanish Italian

HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; IDU, Intravenous Drug User; LYG, Life Years Gained; QALY, Quality-Adjusted Life Year; QoL, Quality of Life; RBV, Ribavirin; SOF, Sofosbuvir; TE, Treatment-Experienced; TN, Treatment-naïve

The full publication of any articles that were deemed relevant for full-text review was obtained. As before, two independent researchers reviewed each full-text article and, in the instance of any disagreement, a third party was consulted. A total of 112 articles were included in this stage of the review (53 articles in the original review and 59 articles in the update) and were then data extracted. The flowchart of the review is illustrated in Figure 19.

Figure 19 Flow-chart for economic systematic review



The search in PubMed retrieved 327 results. The search in EMBASE retrieved 1094 results. The search in CRD retrieved 415 results. A total of 1,836 articles were retrieved by the search. After the duplicates were removed 1,475 abstracts were available to be reviewed against the criteria outlined in Table 37 and 1,166 papers were excluded. After the abstracts were reviewed 316 papers were ordered for full publication review. After the full publications were reviewed 112 papers met the inclusion criteria and data were extracted.

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.

Of the 112 articles that were data extracted, a total of 61 economic evaluations reporting results from decision analytic models in HCV were identified and included from the literature search. They comprised one cost-minimisation analysis, 23 cost-effectiveness analysis and 37 cost-utility analyses. The economic evaluations were conducted in Australia, Brazil, North America (Canada and USA), and Europe (Austria, Belgium, France, Germany, Hungary, Italy, Portugal, Russia, Slovakia, Spain, the UK), with the majority of models based in the US and the UK. A brief overview of all the included economic studies is provided in section **Error! Reference source not found.**.

None of the included studies have evaluated sofosbuvir to date. Six[81-86] studies looked at the cost-effectiveness of screening programmes in HCV and a sole study[87] investigated the economic and clinical impact of an HCV surveillance strategy for cirrhotic HCV patients. Four CUAs[88-91] looked at the impact of initiating treatment at different disease stages on the cost-effectiveness of HCV treatment. Nine studies[92-100] assessed the cost-effectiveness of different treatment regimens/strategies e.g. truncated therapy, delayed-initiation therapy, response-guided therapy, biopsy-guided therapy, multidisciplinary support programme associated therapy etc. Three other studies[101-103] looked at various methodologies of conducting economic evaluations in CHC. Table 38 presents an overview of remaining 38 studies comparing the cost-effectiveness of different treatments.

Table 38 Overview of the studies assessing cost-effectiveness of different treatment

Intervention	Number of studies assessing intervention	No. of studies where intervention was found cost-effective/dominant	References

Intervention	Number of studies assessing intervention	No. of studies where intervention was found cost-effective/dominant	References
BOC+PEG-IFN+RBV	18 studies	Vs. PEG-IFN+RBV: 12 studies	Becker et al., 2012[104], Elbasha et al., 2013[105], Northup et al., 2009[106], Ramachandran et al., 2012[107], Ferrante et al., 2011[108], Mendes et al., 2011[109], Nikoglou et al., 2011[110], Humphreys et al., 2012[111], Mernagh et al., 2012[112], Odhiambo et al.,2012[113], Chan et al., 2013[114], de Ledinghen et al., 2012[115]
		Vs. PEG-IFN-2b+RBV: 3 studies	Ferrante et al., 2013[116], Chhatwal et al., 2013[117], Blazquez-Perez et al., 2013[118]
		Vs. TPV+PEG-IFN+RBV: 3 studies	Ramachandran et al., 2012[107], Fonseca et al., 2012[119], de Ledinghen et al., 2012[115]
		Vs. No treatment: 1 study	Camma et al., 2013[120]
TPV+PEG-IFN+RBV	16 studies	Vs. PEG-IFN+RBV: 11 studies	Cure et al., 2012[121], Northup et al., 2009[106], Ramachandran et al., 2012[107], Jones et al., 2011[122], Gellad et al., 2011[96], Lukac et al., 2012[123], Stahmeyer et al., 2012[124], Chan et al., 2013[114], Jacobson 2012[125], Bock et al., 2013[126], de Ledinghen et al., 2012[115]
		Vs. PEG-IFN-2a+RBV: 3 studies	Brogan et al., 2013[127], Cure et al., 2013[128], Said et al., 2012[129]
		Vs. PEG-IFN-2b+RBV: 1 study	Blazquez-Perez et al., 2013[118]
		Vs. BOC+PEG-IFN+RBV: 2 studies	Camma et al., 2013[120], Cure et al., 2013[128]
		Vs. No treatment: 1 study	Camma et al., 2013[120]
PEG-IFN/RBV/PI (BOC or TPV)	1 study	Vs. PEG-IFN+RBV: 1 study	Liu et al., 2012[130]

Intervention	Number of studies assessing intervention	No. of studies where intervention was found cost-effective/dominant	References
PEG-IFN+RBV	7 studies	Vs. No treatment: 5 studies	Norris et al., 2009[131], Chan et al., 2013[114], Logge et al., 2013[132], Brady et al., 2007[133], Siebert et al., 2009a[103]
		Vs. IFN+RBV: 2 studies	Siebert et al., 2009b[134], Brady et al., 2007[133],
		Vs. BSC: 1 study	Hartwell et al., 2011[135]
PEG-IFN-2a+RBV	4 studies	Vs. PEG-IFN-2b+RBV: 2 studies	Ventayol-Bosch et al., 2010[136], Yeh et al., 2007[137]
		Vs. No treatment: 2 studies	Yeh et al., 2007[137], Grishchenko et al., 2009[138]
		Vs. BSC	Shepherd et al., 2007[139]
PEG-IFN-2b+RBV	2 study	Vs. No treatment: 1 study	Yeh et al., 2007[137]
		Vs. BSC	Shepherd et al., 2007[139]
PEG-IFN-2b	1 study	Vs. BSC	Shepherd et al., 2007[139]

BOC, Boceprevir; BSC, Best Supportive Care; PEG-IFN, Pegylated interferon α; PEG-IFN-2a, Pegylated interferon α - 2a; PEG-IFN-2b, Pegylated interferon α - 2b; RBV, Ribavirin; TPV, Telaprevir

Note: 1) Some studies looked at more than one comparison and thus have been counted more than once; 2) Studies which have not specified IFN-alpha subtype (2a or 2b) have been presented separately

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)[6] or Philips et al. (2004)[7]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

See section **Error! Reference source not found.** (appendix 11)

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

[6] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.
[7] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SmPC/IFU and included in the trials.

This submission includes several de novo economic analyses of chronically infected HCV patients considered suitable candidates for treatment with sofosbuvir. These analyses include:

- Genotype 1 treatment-naïve patients, including those who are interferon eligible or unsuitable for interferon
- Genotype 2 or Genotype 3
    - Treatment-naïve patients, including those who are interferon eligible or unsuitable for interferon
    - Treatment-experienced patients, including those who are interferon eligible or unsuitable for interferon
- Genotype 4/5/6 treatment-naïve patients

The licence for sofosbuvir also covers patients with GT1 infection who are HCV treatment-experienced due to the high unmet need and lack of suitable treatment. However, the SVR for these patients is extrapolated based on an FDA model and as such an economic analysis in this population has not been conducted.

The main economic analyses presented in this section consider the HCV mono-infected populations. As is noted within the licence, it is anticipated that HCV/HIV co-infection population respond in a similar manner to sofosbuvir-based regimens in the mono-infected population with respect to safety and efficacy. The recommended co-administered medicinal product(s) and treatment duration for sofosbuvir combination therapy in the SmPC (table 1 in the SmPC) also match those for the mono infected population.

In PHOTON-1, the HCV/HIV co-infection trial, the use of SOF + RBV for 12 weeks or 24 weeks depending on genotype and treatment-experience, resulted in similar SVR rates when comparing with the use of these regimens/treatment durations in mono-infected populations:

- In treatment-naïve patients with GT1 infection, SOF + RBV for 24 weeks provides similar SVR rates to the same regimen when used in mono-infected patients in SPARE and QUANTUM
- In treatment-naïve patients with GT2 infection comparable responses versus mono-infected populations in FISSION and VALENCE are seen with SOF + RBV for 12 weeks. It should be noted that in PHOTON-1, treatment experienced co-infected patients were treated with 24 weeks SOF + RBV
- Finally in GT3 infection comparable SVR rates are seen with use of the 12-week SOF + PEG-IFN-2a + RBV and the 24-week SOF + RBV regimen, as used in LONESTAR-2 (treatment-naïve) and VALENCE (treatment-experienced) trials respectively.

Furthermore, as observed in mono-infected patients, SVR rates for SOF + RBV regimens in co-infected patients are generally higher or comparable versus PEG-

IFN-2a + RBV comparator regimens (See SVR data input tables in section **Error! Reference source not found.** for co-infected patients).

As such, data inputs and ICERs for HCV/HIV co-infected populations are not split out separately in the main economic analysis but presented in appendix **Error! Reference source not found.**.

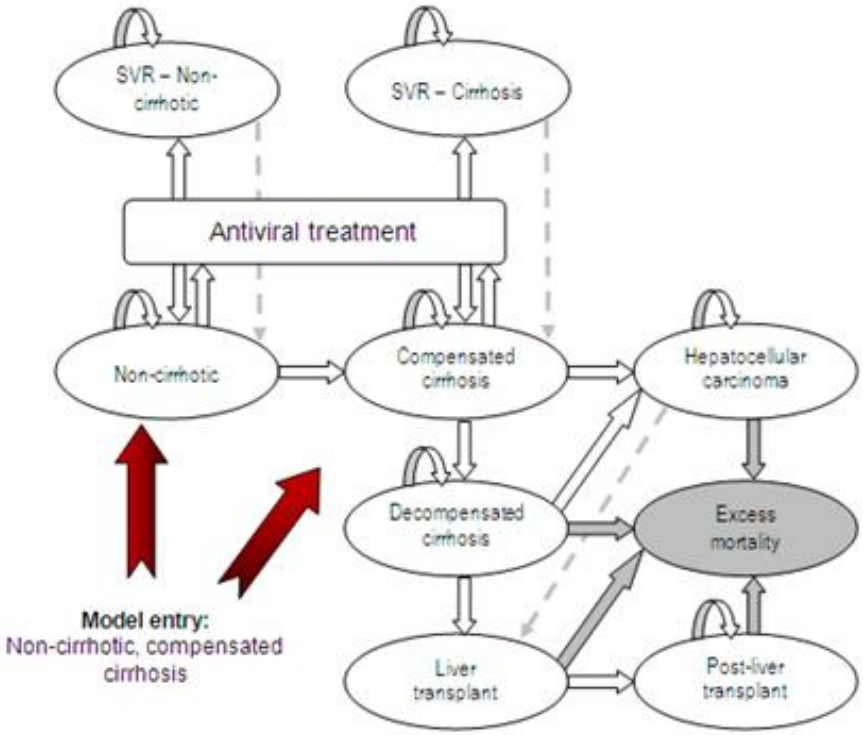
These populations reflect both the licensed indications for sofosbuvir therapy as well as the patients recruited to the phase II and III sofosbuvir studies (i.e. NEUTRINO, FISSON, FUSION, POSITRON, VALENCE, PHOTON 1, QUANTUM, SPARE (11 1 0258), ELECTRON, PROTON and LONESTAR-2).

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

A Markov state-transition model was adapted from the model by Bennett et al., 1997[140] to describe the progression of disease over lifetime and is shown in Figure 20. The same model structure is used for all patients irrespective of HCV genotype or treatment experience. Definitions of the individual health states are provided in Table 39.

Figure 20 Markov model schematic for chronic hepatitis C



Patients can die in each health state. The grey health state “excess mortality” represents the disease-specific mortality associated with having decompensated cirrhosis, liver transplant or hepatocellular carcinoma. Dashed arrows represent health state transitions only investigated in sensitivity analysis

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

This model structure is based on the previous economic models developed by the Southampton Health Technology Assessment Centre (SHTAC) in the UK for NICE (Shepherd et al., 2007[139] and Hartwell et al., 2011[135]). The structure was amended to reflect the data available from the Gilead pivotal phase III randomised clinical trials by combining both mild and moderate chronic hepatitis C patients as non-cirrhotic patients. The structure of the model was consistent both with a coherent theory of the health condition being modelled and with available evidence regarding causal linkages between variables[141]. The Gilead pivotal phase III clinical trials patients were randomised based on cirrhotic and non-cirrhotic status. Study results were reported for the entire cohort as well as non-cirrhotic and cirrhotic cohorts. Based on the study design protocol, no distinction was made between mild and moderate patients. Consequently, it was necessary to pool the mild and moderate health states together as non-cirrhotic patients.

The Gilead trials split patients between non-cirrhotic and cirrhotic defined as per the Fibrotest® and Fibroscan® scores below. No liver biopsy was performed at study entry and therefore liver fibrosis according to the METAVIR score is not available. For some patients, a liver biopsy had been performed within 2 years of screening (and the METAVIR scores for these patients at that time were recorded). However, as patients may have progressed from the time of the biopsy until trial entry and because data were not available for all patients, we could not base the model structure on this data.

According to the conversion between Fibrotest®/Fibroscan® and the METAVIR scores (Table 40), non-cirrhotic patients correspond to F0-F3 while cirrhotic are classified as F4. Therefore, whenever data from the literature was available which reported METAVIR scores, these were included in the model by converting them to non-cirrhotic or cirrhotic using this algorithm. When data was available for mild (F0-F2) and moderate (F3) separately, this data was combined using a 77:23 split between mild and moderate. The 77:23 split was based on the distribution of liver fibrosis obtained from the liver biopsies performed on a subset of the patients included in the Gilead trials.

The model structure displayed in Figure 20 represents the natural history of chronic hepatitis C patients. Non-cirrhotic and cirrhotic patients move to the SVR health state after completing treatment if they have undetectable HCV RNA 12 or 24 weeks after the end of treatment, with all the ensuing costs and health-related quality of life (HRQoL). Non-cirrhotic and cirrhotic patients with a SVR are assumed to no longer face a probability of progressing through the disease as they are considered to have permanently cleared the virus, with no spontaneous reactivation of the HCV infection or re-infection in the base case. Recurrence and re-infection of HCV are however considered in sensitivity analysis for both non-cirrhotic and cirrhotic patients by allowing them to transition to their initial health state following the reappearance of HCV. Patients without a SVR face an annual probability of progressing from no cirrhosis to compensated cirrhosis, as if they had not received antiviral treatment. Although there is some evidence to suggest that antiviral treatment, even in the absence of a SVR, can delay disease progression, we made this simplifying assumption in our model. Patients in both compensated and decompensated cirrhosis stages can progress to hepatocellular carcinoma stage, with its associated costs and HRQoL. Following liver transplantation patients face a probability of dying or moving to the post-transplantation phase. In the post-transplantation phase patients remain at a higher risk of death compared with the general population.

The potential occurrence of decompensated cirrhosis among patients with HCC is ignored since this is expected to have little impact on results, and we have no clinical

or economic data on the impact of developing decompensated cirrhosis among patients with HCC.

Although not represented on the transition diagram, age-specific general population mortality rates are applied to each health state in the model. The risk of death is however highest in the last and most severe states (i.e. decompensated cirrhosis, HCC, liver transplant, post-liver transplantation). The excess mortality associated with these health states is depicted by the grey coloured arrows.

7.2.4 Please define what the health states in the model are meant to capture.

The Markov state-transition model consists of nine states (as defined in Table 39) with transition between the states and costs, mortality and morbidity associated with each state.

Table 39 Model states

State	Definition
Non-cirrhotic patients	Fibroscan® (in countries where locally approved) with a result of ≤12.5 kPa within ≤6 months of Baseline/Day 1[ℓ] Fibrotest® score of ≤0.48 and an APRI of ≤1 performed during screening[ℓ]
Cirrhotic patients	Fibroscan® (in countries where locally approved) showing cirrhosis or results ≥12.5 kPa[ℓ] Fibrotest® score of >0.75 and an AST:platelet ratio index of >2 performed during screening[ℓ]
SVR – Non-cirrhotic	Virological, end of therapy & 12 / 24 weeks
SVR – Cirrhotic	Virological, end of therapy & 12 / 24 weeks
Decompensated cirrhosis	Clinical (major symptomatic)* & histological (cirrhosis)
Hepatocellular carcinoma	Histological
Liver transplantation	Major clinical intervention procedure
Post-liver transplant	Clinical
CHC-attributed death	Absorbing state, attributable death
Background mortality	Mortality rate of the general population (not disease-specific)

SVR, Sustained Virological Response

* Major Symptomatic = Encephalopathy, Coagulopathy, Variceal bleed

ℓ Source: Gilead clinical trials protocols

In the Gilead Phase III trials (NEUTRINO, FISSION, FUSION, POSITRON and VALENCE) the presence of cirrhosis was assessed using the Fibrotest® and Fibroscan®.

The conversion between the Fibrotest®, Fibroscan® and the METAVIR scores is displayed in Table 40.

Table 40 Fibrotest®, Fibroscan® and METAVIR score conversion

METAVIR	Fibrotest®	Fibroscan®
F0	0.00-0.21	2.4 – 7.1 kPa
F0 –F1	0.22-0.27	
F1	0.28-0.31	
F1 – F2	0.32-0.48	7.1 – 9.5 kPa
F2	0.49-0.58	
F2 – F3	0.49-0.58	9.5 – 12.5 kPa
F3	0.59-0.72	
F3 – F4	0.73-0.74	≥ 12.5 kPa
F4	0.75-1.00	

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 captures two distinctive and critical aspects of the condition for patients and clinicians, the on-treatment phase and the off-treatment phase. As shown in Figure 20, cirrhotic or non-cirrhotic patients receiving antiviral treatment can have the virus cleared, depicted by transitioning to the SVR health states. Those who do not clear the virus after treatment remain on their respective health states, or progress to more severe stages of chronic HCV.

The transition probabilities depicting the disease progression were sourced from two latest UK HTAs (Hartwell et al., 2011[135] and Shepherd et al., 2007[139]) and a study by Grishchenko et al., 2009[138], which used estimates of disease progression from the Trent database. According to Grishchenko this database is a reliable source since it is a large representative sample of HCV patients who only attended non tertiary centres in the UK.

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 41 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (until patients reach 100 years of age)	As previous reflected in NICE HTAs, due to the nature of chronic HCV, lifetime horizon allows capturing the difference between sofosbuvir and the comparators in terms of long-term costs and health benefits.	Hartwell et al., 2011[135] Shepherd et al., 2007[139]

Cycle length	Annual (every 3 months for the first 2 years)	Sofosbuvir is administered for either 3 or 6 months (12/24 weeks) which results in SVR12 measured at 6 or 9 months and SVR24 at 9 or 12 months	Hartwell et al., 2011[135] Grishchenko et al., 2009[138] Shepherd et al., 2007[139] Grieve et al., 2006[142] Wright et al., 2006[143]
Half-cycle correction	Applied	Patients transition throughout the cycle and not only at the beginning/end of each cycle. This is also consistent with previous HTAs	Hartwell et al., 2011[135] Shepherd et al., 2007[139]
Were health effects measured in QALYs; if not, what was used?	QALYs	As per NICE reference case	NICE methods 2008[144]
Discount of 3.5% for utilities and costs	Applied	As per NICE reference case	NICE methods 2008[144]
Perspective (NHS/PSS)	NHS and PSS	As per NICE reference case	NICE methods 2008[144]

HCV, Hepatitis C Virus; HTA, Health Technology Assessment; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; PSS, Personal Social Services; QALY, Quality-Adjusted Life Year; SVR, Sustained Virological Response

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?

Sofosbuvir in combination with ribavirin (with/without peginterferon) is compared against telaprevir in combination with peginterferon alfa and ribavirin, boceprevir in combination with peginterferon alfa and ribavirin, peginterferon alfa with ribavirin and best supportive care. Sofosbuvir, telaprevir, boceprevir and peginterferon 2a and ribavirin are implemented in the model as per the marketing authorisations and licensed doses and therefore are directly relevant to the comparison listed in the decision problem. The interventions and comparators used in the model for each genotype are shown below. Previous HTAs and guidelines on treatment for HCV have shown peginterferon 2a to be clinically equivalent to peginterferon 2b[145] and this has been confirmed with clinical advisory board outcomes[146] and clinical trial data in the treatment-naïve population[147;148]. Additionally sofosbuvir trials only utilised peginterferon 2a. The model allows use of both peginterferon 2a and peginterferon 2b, but due to the assumed equivalence of the two treatments, to reflect the sofosbuvir clinical trial data and to ensure the submission is as succinct as possible, only peginterferon 2a is reported within this submission.

Table 42 Treatment strategies per indication

Indication	Active treatment	Comparator(s)
Genotype 1*		
GT1 TN IFN eligible	SOF (400 mg OD) + PEG-IFN-2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12 weeks	Telaprevir (750 mg q8h) + PEG-IFN-2a (180 µg/wk) + weight-based RBV (15 mg/kg OD) for 24 or 48 weeks based on stopping rules and eRVR status
		Boceprevir (800 mg TID) + PEG-IFN-2b (1.5 µg/kg/wk) + weight-based RBV (15 mg/kg OD for 28 or 48 weeks based on futility rules (patients discontinued all study drugs at specific time points if they had detectable HCV RNA)
		PEG-IFN-2a (180 µg/wk) + weight-based RBV (15 mg/kg OD) for 48 weeks
GT1 TN unsuitable for IFN	SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 24 weeks	NT
GT1 TE IFN eligible	*SOF (400 mg OD) + PEG-IFN-2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12 weeks(recommended extending treatment up to 24 weeks)*	*The licence for sofosbuvir also covers GT 1 TE patients. The SVR for these patients was extrapolated based on an FDA model and as such an economic analysis in this population has not been conducted*
Genotype 2		
GT2 TN IFN eligible	SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 12 weeks	PEG-IFN-2a (180 µg/wk) + RBV (800 mg OD) for 24 weeks
GT2 TN unsuitable for IFN	SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 12 weeks	NT
GT2 TE IFN eligible	SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 12 weeks	PEG-IFN-2a (180 µg/wk) + RBV (800 mg OD) for 48 weeks
		NT
GT2 TE unsuitable for IFN	SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 12 weeks	NT
Genotype 3		

Indication	Active treatment	Comparator(s)
GT3 TN IFN eligible	SOF (400 mg OD) + PEG-IFN-2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12 weeks *Alternative regimen* *SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 24 weeks*	PEG-IFN-2a (180 µg/wk) + RBV (800 mg OD) for 24 weeks
GT3 TN unsuitable for IFN	SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 24 weeks	NT
GT3 TE IFN eligible	SOF (400 mg OD) + PEG-IFN-2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12 weeks *Alternative regimen* *SOF (400 mg OD) + weight-based RBV (1,000-1200 mg OD) for 24 weeks*	PEG-IFN-2a (180 µg/wk) + RBV (800 mg OD) for 48 weeks NT
GT3 TE unsuitable for IFN	SOF (400 mg OD) + weight-based RBV (1,000-1200 mg OD) for 24 weeks	NT
Genotype 4/5/6		
GT 4/5/6 TN	SOF (400 mg OD) + PEG-IFN-2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12 weeks	PEG-IFN-2a (180 µg/wk) + weight-based RBV (15 mg/kg OD) for 48 weeks

µg, Microgram; FDA, Food and Drug Administration; GT, Genotype; mg, Milligram; NT, No Treatment; PEG-IFN-2a, Pegylated interferon α - 2a; PEG-IFN-2b, Pegylated interferon α - 2b; q8h, Every 8 Hours; OD, Once Daily; RBV, Ribavirin; RNA, Ribonucleic Acid; RVR, Rapid Virologic Response; SOF, Sofosbuvir; SVR, Sustained Virological Response; TE, Treatment-Experienced; TN, Treatment-naïve; wk, Week

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) SmPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).

- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Treatment regimens for sofosbuvir differ depending on the genotype of the patient, whether the patient is treatment-naïve or experienced and the other anti-viral drugs added to the regimen (PEG-IFN + RBV or RBV alone). No stopping rules, lead in phase, or additional treatment is considered for sofosbuvir, in line with what was done in the sofosbuvir clinical trials and the SmPC since all patients achieve viral suppression 4 weeks post sofosbuvir treatment. Treatment combinations and length of treatment, dependant on genotype are listed in section 7.2.7:

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Clinical data from sofosbuvir trials, published data and data from external experts were incorporated into the economic model as summarised below.

Table 43 Clinical data implemented in the economic models

Characteristic	Data	Source
Patient characteristics	**Mean age at treatment initiation** **Disease severity distribution (% cirrhotic patients)** **Weight**	**HCV research database[149]**
Treatment characteristics	**SVR rates** **Treatment durations**	**SOF clinical trials and published literature**
Health related	**Relative on-treatment**	**SOF clinical trials (by mapping SF-6D to EQ-5D) and published**

quality of life	**decrements**	**literature**
Adverse events	**Rates of AEs**	**SOF clinical trials and published literature**

AE, Adverse Event; EQ-5D, EuroQol-5 Dimensions; HCV, Hepatitis C Virus; SF-6D, Short Form - 6 Dimensions; SOF, Sofosbuvir; SVR, Sustained Virological Response

Patient characteristics

Patient characteristics, including the percentage of patients who are cirrhotic, mean age at treatment, and mean weight, are presented for each indication in Table 44. The proportion of non-cirrhotic patients was defined as 100% minus the proportion of cirrhotic patients, which was obtained from the HCV UK research database querying 5000 anonymised patient records in the UK to reflect real-life practice.[149] This also reflected a conservative approach compared to expert opinion which suggested that the cirrhotic population was significantly higher, particularly in the GT3 population where it was deduced that up to 50% of patients were likely to be cirrhotic. The proportion of non-cirrhotic and cirrhotic patients was varied in the deterministic sensitivity analysis (DSA) for all indications. Finally the mean age at treatment and weight are based on Hartwell et al., 2011[135].

Treatment characteristics

The SVR rate of sofosbuvir for each patient group was obtained from the corresponding sofosbuvir head-to-head trials. The SVR rate of each comparator was derived from sofosbuvir trials where possible; otherwise, relevant literature identified in the systematic literature review (SLR) was used. Details of the calculation and data source are presented from Table 45 to Table 55.

Note: A SLR was also conducted to assess the feasibility of deriving comparative efficacy data (SVR rates) for use in the economic model through a MTC. Whilst we attempted to conduct a MTC for this analysis the results were not robust (as discussed below) and it was considered most appropriate to populate the economic base case with efficacy data from individual studies in all patient groups. The data sources and rationale for these are described further in section 7.3.6.

- Due to the absence of data a MTC network could not be formed for all the populations of interest (i.e. GT 2/3 TE, GT 4/5/6 TN and IFN unsuitable patients)
- For patient groups where an MTC was feasible (TN IFN eligible patients with GT1, GT2 or GT3 infection), these analyses had several limitations
  - Given the structure of the HE model, efficacy data were required split by cirrhotic and non-cirrhotic status, as well as genotype. However this level of information was scarcely reported in the literature. As a result, it was not possible to carry out meta-regressions and subgroup analyses distinguishing between genotype 2 and 3 and cirrhotic status simultaneously. For GT1, it was not feasible to run a meta-regression since sofosbuvir could not be included in the network. In GT1 patients, a network including sofosbuvir was only possible by linking two small phase II trials (i.e. ATOMIC and PROTON) which included only non-cirrhotic patients
  - In addition assumptions had to be made to be able to link the two phase II trials. Since sofosbuvir phase II trials included only non-cirrhotic patients, we had to combine these data with the rest of the literature where the reported

results were based on a combination of cirrhotic and non-cirrhotic patients. For this reason, the meta-regression carried out to provide separate results based on the cirrhotic status of patients did exclude sofosbuvir. A meta-regression was attempted to derive estimates for non-cirrhotic and cirrhotic patients. However, the network on which this analysis was based could not include sofosbuvir, limiting the utility of the GT1 MTC results as inputs for the cost-effectiveness model

- In the phase III clinical trials assessing the efficacy and safey of sofobuvir in GT2 and GT3 naïve patients, it was observed that GT2 and GT3 patients do not have the same expected response to treatment. As a result, the focus of the meta-analysis was to provide results differentiating between GT2 and GT3 patients. However the split by genotype and cirrhotic status is scarcely reported in the literature. In GT2 and GT3 patients the MTC results were based on those obtained for non-cirrhotic and cirrhotic patients combined (i.e. no separate cirrhotic or non-cirrhotic data available) since, as already mentioned previously, the split by both genotype (GT2 and GT3, respectively) and cirrhotic status was not available in the literature. A meta-regression was subsequently conducted to obtain the results for non-cirrhotic and cirrhotic patients separately. However, the results from the meta-regression were for GT2 and 3 combined. To obtain the results for non-cirrhotic and cirrhotic patients split by genotype the following assumptions had to be made: 1) That the meta-analysis results for GT2 and GT3 combined patients were considered for non-cirrhotic patients; 2) The odds ratio between non-cirrhotic and cirrhotic, obtained from the meta-regression for GT2 and 3 combined, was applied to the previous MTC results to obtain the results for cirrhotic patients. Therefore any results obtained are to be used with caution given the fact that the results of two meta-analyses had to be combined to estimate them

- One major limitation of using the results of the MTC for GT3 is that the treatment regimen included in the network (12 weeks of SOF+RBV) is no longer the licensed regimen for this indication (i.e. SOF+PEG-IFN+RBV for 12 weeks or SOF+RBV for 24 weeks)

Given the limitations mentioned above, we are presenting below the results obtained after populating the economic model with efficacy data from individual studies in all patient groups. For completeness and transparency though, we are providing the ERG and NICE with information on the MTC full details and the economic results derived from it in an economic scenario analysis presented in appendix Error! Reference source not found.**.**

The mean treatment durations, obtained from the sofosbuvir trials and the literature, were used to estimate the drug acquisition costs and monitoring costs (whilst on treatment) per patient for each patient group.

HRQoL

The utility decrement associated with sofosbuvir therapy was obtained by using the SF-6D utility decrements derived from SF-36 data, which was collected during the phase III trials. For telaprevir this decrement was also obtained from its phase III clinical trial and was used in their NICE technology appraisal.[146] The utility decrement for boceprevir was that used in their NICE technology appraisal and it was collected from the literature to reflect the relative reduction that anaemia causes in quality of

life during treatment with ribavirin.[150] The utility decrement associated with treatment of peginterferon 2a with ribavirin was obtained from a systematic review. The chosen utility decrement was also used by the latest UK HTAs (Hartwell et al., 2011[135], Shepherd et al., 2007[139]) and was based on a UK trial on mild HCV by Wright et al., 2006[143].

Adverse Events

Rates of Grade 3 and 4 pruritus, diarrhoea and nausea, vomiting, rash, anaemia, thrombocytopenia, neutropenia, and depression from the trials were incorporated into the model so that drug acquisition costs could be assigned for interventions associated with managing these side effects.

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.

The transition probabilities (TPs) used in the model are displayed in Table 44. A table with all the TPs identified from the systematic literature review and the latest HTAs as potentially suitable for the model are presented in section **Error! Reference source not found.**. The transition probabilities chosen for the current model were those also used by the latest UK HTAs (Hartwell et al., 2011[135], Shepherd et al., 2007[139]) and those used by Grishchenko et al., 2009[138], which were taken from a large representative sample of UK cases centres.

The TPs of non-cirrhotic to cirrhotic were derived from Thompson et al., 2008[151], which were also used by Grishchenko et al., 2009[138]. Below are the steps followed to calculate the transition probabilities by indication and age:

- TPs from mild to moderate and moderate to cirrhotic stage were obtained from Thompson et al., 2008[151]. These estimates were available for GT1 and non GT1 for 30, 40, and 50 years

- For mono-infected patients a three- state Markov model was run for 10,15 and 20 years where patients moved from mild to moderate and then from moderate to cirrhotic stage by applying these TPs. Based on a post-hoc weighted distribution of patients across the F0-F2 (mild) and F3 (moderate) stages of disease in the sofosbuvir trials (based on conversion to METAVIR staging from Fibrotest/Fibroscan scores where available) 77% of patients started the Markov model in the mild state and 23% of the patients started the model in the moderate state. The numbers of patients ending in the cirrhotic stage at the end of 10, 15 and 20 years was then estimated

- Another Markov model was developed that considered only the non-cirrhotic and cirrhotic states (two-state model) to reflect the final economic model structure adopted for this submission

- Solver software was then used to obtain the transition probability from non-cirrhotic to cirrhotic for the two-state Markov model so that the number of patients in the cirrhotic stage at the end of follow-up period was equal in the two Markov models. The transition probabilities were obtained for a follow-up period of 10, 15 and 20 years. The two-state Markov model was then rerun using the three different transition probabilities. The root mean square deviation (RMSD) for the difference between the numbers of patients in the cirrhotic state in the two- and three-state Markov model was then estimated.

The transition probabilities for the transition between non-cirrhotic to cirrhotic selected for each age at treatment were the ones resulting in the lowest RMSD.

Patients in the model are also at risk of death from causes other than HCV. All-cause mortality by age group was obtained from the Office for National Statistics[152].

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.

The model allows the TPs from non-cirrhotic to cirrhotic health states to vary by age and genotype according to published literature[153-158] (section 7.3.2). Previous economic evaluations and HTAs also indicated that TPs between advanced health states are not age-dependent[135;139;142;143]. Therefore, TPs from cirrhotic to more advanced health states in the model remain constant. In addition, all-cause mortality was also considered to reflect increased probability of death with age (Table 44).

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?

Not applicable

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[8]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[8] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The model structure, assumptions, inputs and results were discussed and validated with two external clinical experts (a senior consultant and a nurse specialist) from England. Both clinical experts were selected based upon their roles within the NHS as clinical leads at a regional CHC treatment centre that treats >100 CHC patients per year.

The core assumptions that the clinical experts were asked to assess were based upon monitoring and treatment of grade 3 and 4 adverse events only where relevant literature was unavailable. The medium used to collect these assumptions was through direct interview. The outputs were then validated to ensure they were consistent with current practice within two advisory boards discussions incorporating an average of 8 clinical experts.

The clinical experts approached have previously attended advisory boards with Gilead Sciences Ltd. They have also previously attended advisory boards run by Janssen, MSD, Abbvie, Boehringer Ingelheim and Bristol Myers Squibb.

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.

A list of all variables included in the analysis is shown in the tables below. Please note that utility and cost inputs are reported in section 7.4 and 7.5, respectively.

Table 44 Summary of generic variables applied in the economic model

Variable	Value			Reference to section in submission
Patient characteristic	***% cirrhotic patients[a]***	***Mean age at treatment (years)[b]***	***Mean weight (kg)[b]***	
Genotype 1				section 7.3.1, DSA (section 7.6.2) and PSA (section 7.6.3)
GT1 TN IFN eligible	19.0%	45	79	
GT1 TN unsuitable for IFN	19.0%	45	79	
Genotype 2				
GT2 TN IFN eligible	18.0%	40	79	
GT2 TN unsuitable for IFN	18.0%	45	79	
GT2 TE IFN eligible	18.0%	45	79	
GT2 TE unsuitable for IFN	18.0%	45	79	
Genotype 3				
GT3 TN IFN eligible	24.0%	40	79	
GT3 TN unsuitable for IFN	24.0%	45	79	
GT3 TE IFN eligible	24.0%	45	79	
GT3 TE unsuitable for IFN	24.0%	45	79	
Genotype 4/5/6				

Variable	Value			Reference to section in submission
GT 4/5/6 TN	21.0%	45	79	
Transition probabilities	***Transition probabilities, annual***	***Source/ comments***		
Non-cirrhotic to compensated cirrhosis	Mono-infected GT1 30 years: 0.006 40 years: 0.010 50 years: 0.016 Non-GT1 30 years: 0.009 40 years: 0.014 50 years: 0.025	Mono-infected Thomson et al. 2008[151] (used by Grishchenko et al., 2009)[138]		Sections 7.2.5, 7.3.2, DSA (section 7.6.2) and PSA (section 7.6.3)
Non-cirrhotic, SVR to: • non-cirrhotic, recurrence • non-cirrhotic, re-infection	For both health states: Base case: 0 Min: 0 Max: 0.01	External expert opinion, based on the assumption that 1% of patients experience recurrence or reinfection		DSA (section 7.6.2) and PSA (section 7.6.3)
Compensated cirrhosis to: • decompensated cirrhosis • HCC	 0.039 0.014	Fattovich et al., 1997[151] (used by Wright et al., 2006[143], Hartwell et al., 2011[135], and Shepherd et al., 2007[139])		
Compensated cirrhosis, SVR to: • Compensated cirrhosis, recurrence • Compensated cirrhosis, re-infection	For both health states: Base case: 0 Min: 0 Max: 0.01	External expert opinion		

Variable	Value			Reference to section in submission
Decompensated cirrhosis to: • HCC • Liver transplant • Death	 0.014 0.03 0.13	Fattovich et al., 1997[151] (used by Wright et al., 2006[143], Hartwell et al., 2011[135], and Shepherd et al., 2007[139])		
HCC to liver transplant	Base case: 0 Min: 0 Max: 0.01	External expert opinion		
HCC to death	0.43	Fattovich et al., 1997[151] (used by Wright et al., 2006[143] and Hartwell et al., 2011[135])		
Liver transplant to death, Year 1	0.21	Shepherd et al., 2007[139]		
Post-liver transplant to death, Year 2	0.057	Shepherd et al., 2007[139]		
Probability of death by age (all-cause mortality)[c]	***Annual***	***3-month[d]***	***Source***	
25-34	0.000525	0.000131	ONS 2011[152] Calculated as the average of male and female 2011 age-specific mortality rates per 1,000 population	Section 7.3.2, DSA (section 7.6.2) and PSA (section 7.6.3)
35-44	0.001174	0.000294		
45-54	0.002622	0.000656		
55-64	0.006479	0.001624		
65-74	0.016561	0.004166		
75-84	0.047676	0.012138		
85 and over	0.135540	0.035758		

DSA, Deterministic Sensitivity Analysis; GT, Genotype; HCC, Hepatocellular Carcinoma; IFN, Interferon; kg, Kilogram; ONS, Office of National Statistics; PSA, Probabilistic Sensitivity Analysis; SVR, Sustained Virological Response; TE, Treatment-Experienced; TN, Treatment-naïve

[a] HCV UK research database[149]

[b] Hartwell et al., 2011[135]

[c] All-cause mortality is only applicable to patients over 30-year-old since this is a silent disease and its diagnose is usually late

[d] Obtained by converting mortality rates to annual and quarterly probabilities, respectively, using the formula p = 1-exp(-rt), where p = probability, r = rate, and t = time

Table 45 Summary of genotype and treatment-specific variables applied in the economic model – GT1 TN IFN eligible

Variable	**Value**			**Reference to section in submission**
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source/ comments***	
SOF+PEG-IFN-2a+RBV (12 weeks)	91.7% (220/240)	80.8% (42/52)	SVR-12 from NEUTRINO (SmPC)	Section 7.3.1
PEG-IFN-2a+RBV (48 weeks)[a]	43.6% (376/862)	23.6% (26/110)	SVR-24 from McHutchison et al., 2009[159] (Table 2)	
TELAPREVIR+PEG-IFN-2a+RBV[b]	75.4% (109+117+32)/(134+156+52)	61.9% (13/21)	SVR-24 from Telaprevir NICE STA (Figure 6 , page 60)[146]	
BOCEPREVIR+PEG-IFN-2b+RBV[c]	64.1% (387/604)	55.0% (33/60)	SVR-24 from Lawitz et al., 2012 (AASLD 2012[160])	

Variable	Value			Reference to section in submission
Treatment Duration – Completed Treatment				
Strategy	***% patients***	***weeks***	***Source***	
SOF+PEG-IFN-2a+RBV	XXXXXXXXXX	12.0	NEUTRINO	
PEG-IFN-2a+RBV	60%	48.0	McHutchison et al., 2009[161]	
Telaprevir+PEG-IFN-2a+RBV	53.7% (195/363) 20.1% (73/363)	24.0 48.0	Jacobson et al., 2011[162] (figure 1, eRVR positive T12PR group 24 wks and eRVR negative T12PR group 48 wks)	
Boceprevir+PEG-IFN-2b+RBV	44.0% 22.3% (82/368)	28.0 48.0	Poordad et al. 2011[163] (SPRINT-2) (HCV RNA undetectable at week 8-24, page 1195, and HCV RNA not undetectable at week 8-24, page 1200)	
Treatment Duration – Discontinued due to AEs[d]				
Strategy	***% patients***	***weeks***	***Source***	
SOF+PEG-IFN-2a+RBV	XXXXXXX	XXX	NEUTRINO	
PEG-IFN-2a+RBV	13.0%	24.0[f]	McHutchison et al., 2009[161]	
Treatment Duration – Discontinued due to other reasons				
Strategy	***% patients[e]***	***weeks***	***Source***	
SOF+PEG-IFN-2a+RBV	XXXXXXX	XXX	NEUTRINO	
PEG-IFN-2a+RBV	24.0%	24.0[f]		
Telaprevir+PEG-IFN-2a+RBV	23.2%	18.0[f]		
Boceprevir+PEG-IFN-2b+RBV	26.1%	24.0	Assumed equal to the average number of weeks due to futility rules	
Treatment Duration – Discontinued due to stopping/futility rules				

Variable	Value				Reference to section in submission
Strategy	***% patients***	***weeks***	***Source***		
SOF+PEG-IFN-2a+RBV	NA	NA			
PEG-IFN-2a+RBV	NA	NA			
Telaprevir+PEG-IFN-2a+RBV	1.7%	4.0	Jacobson et al., 2012[164] (Up to week 4)		
	1.3% (3%-1.7%)	12.0	Jacobson et al., 2011[162] (Up to week 12, 3% collected from page 2410)		
Boceprevir+PEG-IFN-2b+RBV	7.6% (24/316)	24.0	Poordad et al. 2011[163] (page 1199 and 1201)		
AE incidence (Grade 3/4)[g]	***SOF+PEG-IFN-2a+RBV (%)***	***PEG-IFN-2a+RBV (%)***	***Telaprevir+PEG-IFN-2a+RBV (%)***	***Boceprevir+PEG-IFN-2b+RBV (%)***	
Nausea	0.0%	1.0%	1.0% (13/1346)	0.0%	Section 6.9
Vomiting	0.3% (1/327)	0.0%	0.0%	0.0%	
Diarrhoea	0.0%	0.0%	0.0%	0.0%	
Pruritus	0.0%	0.1%	1.3% (17/1346)	0.0%	
Rash	0.3% (1/327)	0.1%	4.8% (65/1346)	0.0%	
Anaemia	2.14% (7/327)	24.9% ((5+85)/(21+340))	49.3% ((55+2+377+11)/(82+821))	0.8% (3/368)	
Thrombocytopenia	0.3% (1/327)	0.6% (0+1+1+0)/(21+34)	2.6% (10+1+12+0)/(82+821)	0.0%	
Neutropenia	7.0% (23/327)	14.7% (4+0+39+10)/(21+340)	10.3% (8+2+72+11)/(82+821)	0.3% (1/368)	
Depression	0.3% (1/327)	0.3% (1/368)	0.0%	0.3% (1/368)	

AE, Adverse Event; PEG-IFN-2a, Pegylated interferon α - 2a; PEG-IFN-2b, Pegylated interferon α - 2b; RBV, Ribavirin; SOF, Sofosbuvir; STA, Single Technology Appraisal; wk, Week

[a] This study was selected from the clinical systematic literature review as it was the most recent publication with relevant data. Roberts et al. 2009[165] could have been used as it provided SVRs for F0-F3 and F4 patients; however, the SVRs for F4 patients were considered unrealistically low. Mach et al. 2010[166] and Neri et al. 2010[167] were another possibility but it considered only the subtype of GT1b patients

[b] The SVRs from the Telaprevir STA were used as the data was split between non-cirrhotic and cirrhotic patients. While this STA was not included in the list of articles of the base case meta-analysis, it was considered in a sensitivity analysis

[c] The SVRs from this poster were used as they were split between non-cirrhotic and cirrhotic. No other source was found that provided this split. As no publication was found with the data reported in this poster these data was not included in the meta-analysis

[d] Telaprevir and boceprevir discontinuation due to adverse events (9.9% [36/363] and 12.2% [45/368], respectively) is included in discontinuation due to other reasons, as reported in Jacobson et al., 2011[162] and McHutchison et al., 2009[161] (supplementary appendix)

[e] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs or due to the stopping rules)

[f] An assumption was made to obtain an average treatment duration similar to that indicated for the telaprevir and PEG-IFN+RBV treatment arms in the telaprevir STA

[g] Sources:

- SOF+PR: NEUTRINO
- PEG-IFN-2a+RBV: Anaemia/neutropenia/thrombocytopenia: Kauffman et al., 2011 (ADVANCE, grade 3 and 4 adverse events)[168]; Other: FDA (Table 32)[169]
- Telaprevir+PR: Anaemia/neutropenia/thrombocytopenia: Kauffman et al., 2011[168] (grade 3 and 4 adverse events); Rash: Cacoub et al., 2012[170]; Other: FDA (Table 32)[169]
- Boceprevir+PR: Poordad et al., 2011[163] (Table S2C in the Supplement, serious adverse events as grade 3 and 4 were not published or reported in the Boceprevir submissions)

Table 46 Summary of genotype and treatment-specific variables applied in the economic model – GT1 TN unsuitable for IFN

Variable	Value	Reference to section in submission

Variable	Value			Reference to section in submission
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source***	
SOF+RBV (24 weeks) No treatment	67.6% (100/148) 0.0%	36.4% (4/11) 0.0%	SVR-12 from QUANTUM and SPARE (11 1 0258) (SmPC)	Section 7.3.1
Treatment Duration	***SOF+RBV (24 weeks)***	***Source***		
Completed Treatment (% patients)	XXXX	QUANTUM		
Completed Treatment (weeks)	XX			
Discontinued due to AEs (% patients)	XXXX			
Discontinued due to AEs (weeks) [a]	XX			
Discontinued due to other reasons (% patients) [b]	XXX			
Discontinued due to other reasons (weeks)	XX			
AE incidence[c]	***SOF+RBV (%)***			
Nausea	0.0%			
Vomiting	0.4% (1/250)			
Diarrhoea	0.0%			
Pruritus	0.0%			
Rash	0.0%			
Anaemia	0.8%(2/250)			
Thrombocytopenia	0.0%			

Variable	Value	Reference to section in submission
Neutropenia	0.0%	
Depression	0.0%	

AE, Adverse Event; RBV, Ribavirin; SOF, Sofosbuvir; SVR, Sustained Virological Response

[a] Assumption

[b] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs)

[c] VALENCE; GT3 treatment-naïve 24 weeks (as the required breakdown was not available from QUANTUM)

Table 47 Summary of genotype and treatment-specific variables applied in the economic model – GT2 TN IFN eligible

Variable	Value			Reference to section in submission
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source***	
SOF+RBV (12 weeks)	96.7% (29+59)/(30+61)	85.7% (2+10)/(2+12)	SVR-12 from VALENCE and FISSION (SmPC)	Section 7.3.1
PEG-IFN-2a+RBV (24 weeks)	81.5% (44/54)	61.5% (8/13)	SVR-24 from FISSION	

Variable	Value		Reference to section in submission
Treatment Duration[a]	***SOF+RBV***	***PEG-IFN-2a+RBV***	
Completed Treatment (% patients)	XXX	XXXX	
Completed Treatment (weeks)	XX	XX	
Discontinued due to AEs (% patients)	XXX	XXXX	
Discontinued due to AES (weeks)	XX	XXX	
Discontinued due to other reasons (% patients)[b]	XXX	XXX	
Discontinued due to other reasons (weeks)	XX	XXX	
AE incidence (Grade 3/4)[a]	***SOF+RBV (%)***	***PEG-IFN-2a+RBV (%)***	
Nausea	0.4% (1/256)	0.4% (1/243)	Section 6.9
Vomiting	0.0%	0.0%	
Diarrhoea	0.0%	0.0%	
Pruritus	0.0%	0.0%	
Rash	0.0%	0.0%	
Anaemia	0.6% ((1+1)/(256+84))	0.8% (2/243)	
Thrombocytopenia	0.0%	2.1% (5/243)	
Neutropenia	0.0%	3.3% (8/243)	
Depression	0.0%	0.4% (1/243)	

AE, Adverse Event; PEG-IFN-2a, Pegylated interferon α - 2a; RBV, Ribavirin; SOF, Sofosbuvir; SmPC, Summary of Product Characteristics; SVR, Sustained Virological Response

[a] Source:

- SOF+RBV: VALENCE and FISSION; In VALENCE AEs were reported for GT2, GT3, TN and TE patients combined

- PEG-IFN-2a+RBV: FISSION

[b] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs)

Table 48 Summary of genotype and treatment-specific variables applied in the economic model – GT2 TN unsuitable for IFN

Variable	Value			Reference to section in submission
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source***	
SOF+RBV (12 weeks)	93.4% ((29+85)/(30+92))	94.7% ((2+16)/(2+17))	SVR-12 from VALENCE and POSITRON (SmPC)	Section 7.3.1
No treatment	0.0%	0.0%		
Treatment Duration	***SOF+RBV***	***Source***		
Completed Treatment (% patients)	XXX XXXXX	VALENCE and POSITRON		
Completed Treatment (weeks)	XX			
Discontinued due to AEs (% patients)	XXXXXXXXXXX			
Discontinued due to AES (weeks)	XXX			
Discontinued due to other reasons (% patients)[a]	XXX			
Discontinued due to other reasons (weeks)	XXX			
AE incidence	***SOF+RBV (%)***	***Source***		
Nausea	0.0%	VALENCE and POSITRON; In VALENCE AEs were reported for GT2, GT3, TN and TE patients combined		Section 6.9
Vomiting	0.0%			
Diarrhoea	0.0%			

Variable	Value		Reference to section in submission
Pruritus	0.0%		
Rash	0.0%		
Anaemia	0.3% ((0+1)/(207+84))		
Thrombocytopenia	0.0%		
Neutropenia	0.0%		
Depression	0.0%		

AE, Adverse Event; GT, Genotype; RBV, Ribavirin; SOF, Sofosbuvir; SVR, Sustained Virological Response; TE, Treatment-Experienced; TN, Treatment-naïve

[a] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs)

Table 49 Summary of genotype and treatment-specific variables applied in the economic model – GT2 TE IFN eligible

Variable	Value			Reference to section in submission
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source/ Comments***	
SOF+RBV (12 weeks)	91.5% (30+24)/(33+26)	82.4%(7+7)/(8+9)	SVR-12 from VALENCE and FUSION (SmPC)	Section 7.3.1

Variable	Value			Reference to section in submission
PEG-IFN-2a+RBV (48 weeks)[a]	35.0% (62.5%*53%+37.5%*5%)	35.0% (62.5%*53%+37.5%*5%)	SVR-24 from Lagging et al.,2013[171] and Shoeb et al.,2011[172] (see appendix **Error! Reference source not found.** for calculations); SVRs are for GT2 and GT3 combined (in Lagging these corresponded to 18% and 82%, respectively); data is for non-cirrhotic and cirrhotic combined as no split was provided	
No treatment	0%	0%		
Treatment Duration[b]	***SOF+RBV***		***PEG-IFN-2a+RBV***	
Completed Treatment (% patients)	XXX		63.2% (24/38)	
Completed Treatment (weeks)	XX		48.0	
Discontinued due to AEs (% patients)	XXXX		36.8% (14/38)	
Discontinued due to AEs (weeks)	XX		24.0[c]	
Discontinued due to other reasons (% patients)[d]	XXXX		0.0%	
Discontinued due to other reasons (weeks)	XX		NA	
AE incidence (Grade 3/4)[b]	***SOF+RBV (%)***		***PEG-IFN-2a+RBV (%)***	
Nausea	0.0%		0.4% (1/243)	Section 6.9
Vomiting	0.0%		0.0%	
Diarrhoea	0.0%		0.0%	
Pruritus	0.0%		0.0%	

Variable	Value		Reference to section in submission
Rash	0.0%	0.0%	
Anaemia	1.6% ((1+2)/(84+103))	0.8% (2/243)	
Thrombocytopenia	0.0%	2.1% (5/243)	
Neutropenia	0.0%	3.3% (8/243)	
Depression	0.0%	0.4% (1/243)	

AE, Adverse Event; EPO, Erythropoietin; PEG-IFN, Pegylated interferon α; QoL, Quality of Life; SF-6D, Short Form - 6 Dimensions; SOF, Sofosbuvir; STA, Single Technology Appraisal; wk, Week

[a] These studies were selected for PEG-IFN-2a because no other publications were found with appropriate data on PEG-IFN-experienced patients

[b] Source:

- SOF+RBV: VALENCE and FUSION; In VALENCE AEs were reported for GT2, GT3, TN and TE patients combined
- PEG-IFN-2a+RBV: FISSION

[c] Assumed equal to PEG-IFN + RBV in GT1 TN IE

[d] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs)

Table 50 Summary of genotype and treatment-specific variables applied in the economic model – GT2 TE unsuitable for IFN

Variable	Value			Reference to section in submission
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source/ Comments***	
SOF+RBV (12 weeks)	92.0% (30+85)/(33+92)	92.0% (7+16)/(8+17)	SVR-12 from VALENCE and POSITRON (SmPC)	Section 7.3.1
No treatment	0.0%	0.0%		

Variable	Value		Reference to section in submission
Treatment Duration	***SOF+RBV***	***Source/ Comments***	
Completed Treatment (% patients)	XXXX	VALENCE and POSITRON	
Completed Treatment (weeks)	XX		
Discontinued due to AEs (% patients)	XXX		
Discontinued due to AES (weeks)	XX		
Discontinued due to other reasons (% patients)[a]	XXX		
Discontinued due to other reasons (weeks)	XX		
AE incidence	***SOF+RBV (%)***	***Source/ Comments***	
Nausea	0.0%	VALENCE and POSITRON; In VALENCE AEs were reported for GT2, GT3, TN and TE patients combined	Section 6.9
Vomiting	0.0%		
Diarrhoea	0.0%		
Pruritus	0.0%		
Rash	0.0%		
Anaemia	0.3% ((0+1)/(207+84))		
Thrombocytopenia	0.0%		
Neutropenia	0.0%		
Depression	0.0%		

AE, Adverse Event; EPO, Erythropoietin; PEG-IFN, Pegylated interferon α; SOF, Sofosbuvir; STA, Single Technology Appraisal; wk, Week

[a] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs)

Table 51 Summary of genotype and treatment-specific variables applied in the economic model – GT3 TN IFN eligible

Variable	Value			Reference to section in submission
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source/ Comments***	
SOF+PEG-IFN-2a+RBV (12 weeks)	97.4% (38/39)	83.3% (10/12)	Average SVR-12 from ELECTRON and PROTON (SmPC) ELECTRON and PROTON did not include non-cirrhotic patients; therefore LONESTAR-2 data was used	Section 7.3.1
SOF+RBV (24 weeks)	93.5% (86/92)	92.3%(12/13)	SVR-12 from VALENCE (SmPC)	
PEG-IFN-2a+RBV (24 weeks)	71.2% (99/139)	29.7% (11/37)	SVR-24 from FISSION (SmPC)	
Treatment Duration[a]	***SOF+PEG-IFN-2a+RBV (12 weeks)***	***SOF+RBV (24 weeks)***	***PEG-IFN-2a+RBV***	
Completed Treatment (% patients)	XXXX	XXXXXXXXX	XXXXXXXX	
Completed Treatment (weeks)	XX	XX	XX	
Discontinued due to AEs (% patients)	XXX	XXXXXXXXX	XXXXXXXX	
Discontinued due to AES (weeks)	XX	XXX	XXX	
Discontinued due to other reasons (% patients)[b]	XXX	XXXX	XXX	
Discontinued due to other reasons (weeks)	XX	XXX	XXX	
AE incidence (Grade 3/4)[c]	***SOF+PEG-IFN+RBV (12 weeks)***	***SOF+RBV (24 weeks)***	***PEG-IFN+RBV***	

Variable	Value			Reference to section in submission
Nausea	0.0%	0.0%	0.4% (1/243)	Section 6.9
Vomiting	0.3% (1/327)	0.4% (1/250)	0.0%	
Diarrhoea	0.0%	0.0%	0.0%	
Pruritus	0.0%	0.0%	0.0%	
Rash	0.3% (1/327)	0.0%	0.0%	
Anaemia	2.1% (7/327)	0.8% (2/250)	0.8% (2/243)	
Thrombocytopenia	0.3% (1/327)	0.0%	2.1% (5/243)	
Neutropenia	7.0% (23/327)	0.0%	3.3% (8/243)	
Depression	0.3% (1/327)	0.0%	0.4% (1/243)	

AE, Adverse Event; EPO, Erythropoietin; PEG-IFN, Pegylated interferon α; SOF, Sofosbuvir; STA, Single Technology Appraisal; wk, Week

[a] Source:

- SOF+PEG-IFN-2a+RBV: Average from ELECTRON and PROTON
- SOF+RBV: VALENCE; Average number of weeks for discontinuation due to AEs and other reason obtained from CSR, Table 4 in appendix assuming patients discontinued in the middle of each interval
- PEG-IFN-2a+RBV: FISSION

[b] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs)

[c] Source:

- SOF+PEG-IFN-2a+RBV: Assumed equal to NEUTRINO (as the required breakdown was not available from ELECTRON and PROTON)
- SOF+RBV: VALENCE
- PEG-IFN-2a+RBV: FISSION

Table 52 Summary of genotype and treatment-specific variables applied in the economic model – GT3 TN unsuitable for IFN

Variable	Value			Reference to section in submission
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source/ Comments***	
SOF+RBV (24 weeks)	93.5% (86/92)	92.3% (12/13)	SVR-12 from VALENCE (SmPC)	Section 7.3.1
No treatment	0%	0%		
Treatment Duration	***SOF+RBV***		***Source/ Comments***	
Completed Treatment (% patients)	XXXXXXX		VALENCE	
Completed Treatment (weeks)	XXX			
Discontinued due to AEs (% patients)	XXXXXXX			
Discontinued due to AES (weeks)	XXX			
Discontinued due to other reasons (% patients)[a]	XXX			
Discontinued due to other reasons (weeks)	XXX			
AE incidence	***SOF+RBV (%)***		***Source/ Comments***	
Nausea	0.0%		VALENCE	Section 6.9
Vomiting	0.4% (1/250)			

Variable	Value		Reference to section in submission
Diarrhoea	0.0%		
Pruritus	0.0%		
Rash	0.0%		
Anaemia	0.8% (2/250)		
Thrombocytopenia	0.0%		
Neutropenia	0.0%		
Depression	0.0%		

AE, Adverse Event; EPO, Erythropoietin; RBV, Ribavirin; RVR, Rapid Virologic Response; SOF, Sofosbuvir; SmPC, Summary of Product Characteristics; SVR, Sustained Virological Response

[a] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs)

Table 53 Summary of genotype and treatment-specific variables applied in the economic model – GT3 TE IFN eligible

Variable	Value			Reference to section in submission
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source/ Comments***	
SOF+PEG-IFN-2a+RBV (12 weeks)	83.3% (10/12)	83.3% (10/12)	SVR-12 from LONESTAR-2 (SmPC)	Section 7.3.1
SOF+RBV (24 weeks)	85.0% (85/100)	60.0% (27/45)	SVR-12 from VALENCE (SmPC)	

Variable	Value			Reference to section in submission
PEG-IFN-2a+RBV (48 weeks)	35.0% (62.5%*53%+37.5%*5%)	35.0% (62.5%*53%+37.5%*5%)	SVR-24 from Lagging et al., 2013 [171] and Shoeb et al.,2011[172] (see appendix **Error! Reference source not found.** for calculations); SVRs are for GT2 and GT3 combined (in Lagging these corresponded to 18% and 82%, respectively); data is for non-cirrhotic and cirrhotic combined as no split was provided	
No treatment	0%	0%		
Treatment Duration[a]	***SOF+PEG-IFN-2a+RBV (12 weeks)***	***SOF+RBV (24 weeks)***	***PEG-IFN-2a+RBV (48 weeks)***	
Completed Treatment (% patients)	XXXXXXX	XXXXXXX	63.2% (24/38)	
Completed Treatment (weeks)	XX	XX	48	
Discontinued due to AEs (% patients)	XXXXXXX	XXXXXXX	36.8% (14/38)	
Discontinued due to AES (weeks)	X	XXX	24.0[c]	
Discontinued due to other reasons (% patients)[b]	XXXX	XXX	0.0%	
Discontinued due to other reasons (weeks)	XX	XXX	NA	
AE incidence (Grade 3/4)[d]	***SOF+PEG-IFN-2a+RBV (12 weeks)***	***SOF+RBV (24 weeks)***	***PEG-IFN-2a+RBV (48 weeks)***	

Variable	Value			Reference to section in submission
Nausea	0.0%	0.0%	0.4% (1/243)	Section 6.9
Vomiting	0.3% (1/327)	0.4% (1/250)	0.0%	
Diarrhoea	0.0%	0.0%	0.0%	
Pruritus	0.0%	0.0%	0.0%	
Rash	0.3% (1/327)	0.0%	0.0%	
Anaemia	2.1%(7/327)	0.8% (2/250)	0.8% (2/243)	
Thrombocytopenia	0.3% (1/327)	0.0%	2.1% (5/243)	
Neutropenia	7.0% (23/327)	0.0%	3.3% (8/243)	
Depression	0.3% (1/327)	0.0%	0.4% (1/243)	

AE, Adverse Event; EPO, Erythropoietin; GT, Genotype; PEG-IFN-2a, Pegylated interferon α - 2a; RBV, Ribavirin; SOF, Sofosbuvir; SmPC, Summary of Product Characteristics; SVR, Sustained Virological Response

[a] Source:

- SOF+PEG-IFN-2a+RBV: LONESTAR-2
- SOF+RBV: VALENCE; Average number of weeks for discontinuation due to AEs and other reason obtained from CSR, Table 4 in appendix assuming patients discontinued in the middle of each interval
- PEG-IFN-2a+RBV: Lagging et al., 2013[171]

[b] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs)

[c] Assumed equal to PEG-IFN + RBV in GT1 TN IE

[d] Source:

- SOF+PEG-IFN-2a+RBV: Assumed equal to NEUTRINO (as the required breakdown was not available from LONESTAR-2)
- SOF+RBV: VALENCE
- PEG-IFN-2a+RBV: FISSION

Table 54 Summary of genotype and treatment-specific variables applied in the economic model – GT3 TE unsuitable for IFN

Variable	Value			Reference to section in submission
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source/ Comments***	
SOF+RBV (24 weeks)	85.0% (85/100)	60.0% (27/45)	SVR-12 from VALENCE (SmPC)	
NT	0.0%	0.0%		
Treatment Duration	***SOF+RBV***		***Source/ Comments***	
Completed Treatment (% patients)	XXXXXXX		VALENCE; Average number of weeks for discontinuation due to AEs and other reason obtained from CSR, Table 4 in appendix assuming patients discontinued in the middle of each interval	
Completed Treatment (weeks)	XXX			
Discontinued due to AEs (% patients)	XXXXXXX			
Discontinued due to AES (weeks)	XXX			
Discontinued due to other reasons (% patients)[a]	XXX			
Discontinued due to other reasons (weeks)	XXX			
AE incidence (Grade 3/4)	***SOF+RBV***		***Source***	
Nausea	0.0%		VALENCE	
Vomiting	0.4% (1/250)			
Diarrhoea	0.0%			
Pruritus	0.0%			
Rash	0.0%			
Anaemia	0.8% (2/250)			

Thrombocytopenia	0.0%		
Neutropenia	0.0%		
Depression	0.0%		

AE, Adverse Event; EPO, Erythropoietin; RBV, Ribavirin; SOF, Sofosbuvir; SmPC, Summary of Product Characteristics; SVR, Sustained Virological Response

[a] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs)

Table 55 Summary of genotype and treatment-specific variables applied in the economic model – GT4/5/6 TN

Variable	**Value**			**Reference to section in submission**
Efficacy	***Initial state SVR % n/N***			
	Non-cirrhotic	***Cirrhotic***	***Source/ Comments***	
SOF+PEG-IFN-2a+RBV (12 weeks)	100% (33/33)	50.0% (1/2)	SVR-12 from NEUTRINO (SmPC)	Section 7.3.1
PEG-IFN-2a+RBV (48 weeks)[a]	50.0% (8/16)	38.6% (50.0%x(44.0%/57.0%))	Non-cirrhotic and cirrhotic: SVR-24 from Manns et al., 2001[173] Cirrhotic: Assuming the increase in SVR between fibrosis/cirrhosis and no/minimal fibrosis is the same across genotypes 1, 2/3 and 4/5/6	

Variable	Value		Reference to section in submission
Treatment Duration[b]	***SOF+PEG-IFN-2a+RBV***	***PEG-IFN-2a+RBV***	
Completed Treatment (% patients)	XXXXXXX	60.0%[c]	
Completed Treatment (weeks)	XX	48	
Discontinued due to AEs (% patients)	XXXXXXX	14.0%	
Discontinued due to AES (weeks)	XX	24.0[c]	
Discontinued due to other reasons (% patients)[d]	XX	26.0%	
Discontinued due to other reasons (weeks)	XX	24.0[c]	
AE incidence (Grade 3/4)[e]	***SOF+RBV (%)***	***PEG-IFN-2a+RBV (%)***	
Nausea	0.0%	0.4% (1/243)	Section 6.9
Vomiting	0.3% (1/327)	0.0%	
Diarrhoea	0.0%	0.0%	
Pruritus	0.0%	0.0%	
Rash	0.3% (1/327)	0.0%	
Anaemia	2.1% (7/327)	0.8% (2/243)	
Thrombocytopenia	0.3% (1/327)	2.1% (5/243)	
Neutropenia	7.0% (23/327)	3.3% (8/243)	
Depression	0.3% (1/327)	0.4% (1/243)	

AE, Adverse Event; EPO, Erythropoietin; PEG-IFN-2a, Pegylated interferon α - 2a; RBV, Ribavirin; SOF, Sofosbuvir; SmPC, Summary of Product Characteristics; SVR, Sustained Virological Response

[a] Only two studies on GT4/5/6 could have been used from those included in the SLR, Manns et al. 2001[173] and Lindsay et al 2001[174]. Manns was chosen over Lindsay because there was a greater number of GT4/5/6 patients in Manns compared with Lindsay

[b] Source:

- SOF+PEG-IFN-2a+RBV: NEUTRINO
- PEG-IFN-2a+RBV: Manns et al, 2001[173]; % patients that discontinued due to AEs taken from page 963

[c] Assumed equal to PEG-IFN + RBV in GT1 TN IE

[d] Calculation (100%-sum of the other categories, that is, patients that completed treatment and discontinued treatment due to AEs)

[e] Source:

- SOF+PEG-IFN-2a+RBV: NEUTRINO; Assumed the same as for GT1
- PEG-IFN-2a+RBV: FISSION

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.

The base case model was based on a lifetime horizon, that is, until patients reached 100 years of age (as utilised in previous HCV NICE HTAs). Long-term consequences (i.e. lifetime costs, life years, quality-adjusted life years, number of deaths avoided, liver transplant avoided, cirrhosis avoided, HCC cases avoided) following the success or not of the treatments (i.e. whether or not patients have reached SVR) were extrapolated by the Markov model. SVR rates on the other hand were not extrapolated as they came directly, either from the literature or clinical trials The only assumption related to SVR was about the concordance stating equivalent SVR rates when assessed 12 or 24 weeks after the end of treatment[175]. As such, SVR-12 has been established as an appropriate endpoint for regulatory approval and is now accepted by all clinical and regulatory authorities (including the EMA).

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Significant model assumptions were made and are listed below. These are compared and discussed against the assumptions made in previous models:

- Patients could enter the model in either the non-cirrhotic or compensated cirrhosis stages of disease. The non-cirrhotic state combines the mild and moderate to reflect the data from the sofosbuvir trials (based on Fibrotest® and Fibroscan®) and the homogeneity of the SVR rates for F0-F3 patients with sofosbuvir regimens[176]. The model allows a combined cohort reflective of the under treater care population in the UK or a scenario of non-cirrhotic and cirrhotic patients to be followed separately. For the purpose of this submission results for a combined cohort are presented as this best represents the overall patient population of interest.

- The previous models by Shepherd et al., 2007[139] and Hartwell et al., 2011[135] assumed patients who achieved a SVR from either mild or moderate chronic HCV have the same risk of developing HCC as the general population. Therefore a zero risk of progression for the non-cirrhotic CHC patients was used for the base case analysis. This is consistent with end of treatment biopsies from previously reported trials that did not find any evidence of disease progression following an SVR[177]. Furthermore, the possibility of recurrence or re-infection in both non-cirrhotic and cirrhotic patients that had reached SVR was permitted.

- Shepherd et al., 2007[139] and Hartwell et al., 2011[135] included as sensitivity analysis the possibility for mild CHC patients to spontaneously reach SVR. This was not taken into account in our model in order to reflect clinical practise.

- Different health states representing decompensated cirrhosis (such as ascites, hepatic encephalopathy and hepatorenal syndrome) were collapsed into one (i.e., like in Shepherd et al., 2007[139] and Hartwell et al., 2011[135] but unlike in Bennett et al., 1997[140]). The advantage of collapsing those states into one is that this better reflects the real world and allows for patients to

have several complications simultaneously. In addition, assigning costs to individual complications and using the average could lead to biased results if complications have substantially different costs and durations. The problem is identical with utilities for calculating quality-adjusted life years (QALYs). For example, if complications with high costs are generally associated with short durations, the model would overestimate the cost of decompensated cirrhosis. In any case, it may be argued that it is not feasible to estimate costs for different types of complications separately since in reality many patients live with several complications simultaneously, and there are interactions between those complications on costs. The recommended approach to use observational data on a representative sample of patients with decompensated cirrhosis (who may suffer different complications or combinations of complications) has been adopted by Wright et al., 2006[143] in particular.

- All patients in the decompensated cirrhosis health state are assumed to be candidates for liver transplantation.

- Only patients that did not achieve SVR may progress to more advanced stages of the disease. That is, patients do not progress while on treatment nor during the 12 to 24 weeks after the end of treatment.

- During treatment, patients are assumed to experience a decrement in HRQoL resulting from treatment adverse events.

- Patients do not die during the treatment period. Age-specific general population mortality rates are applied to all health states in the model.

- Transition probabilities from non-cirrhotic to cirrhotic are based on age at treatment.

- Background mortality is assumed to be the same as for the general population

- While patients with compensated cirrhosis that achieve SVR are followed-up over a lifetime (and therefore follow-up costs are applied during that time period), non-cirrhotic patients with SVR are only followed until the end of year two. Patients who achieve an SVR experience an improvement over their baseline HRQoL.

- No patients move from the HCC health state to the LT health state. Patient movement between these health states is tested in the sensitivity analysis based on feedback from external expert opinion.

Some of these assumptions are tested in a sensitivity analysis and discussed in more detail in section 7.6. They have also been confirmed as appropriate in KOL discussions (see section 7.3.5 for a detailed description of the involvement of clinical experts in the development of the economic model).

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

HCV infection is associated with lower levels of HRQoL relative to the general population and significantly higher levels of absenteeism, presenteeism, overall work impairment, and activity impairment (Di Bonaventura et al., 2010[178]). Reported HRQoL impairment is higher in CHC patients compared with other liver diseases as well as other chronic diseases such as type II diabetes and irritable bowel syndrome (Kallman et al., 2007[179]; Mikocka-Walus et al., 2008[180]).

Treatment itself can pose an additional burden on the patient by reducing HRQoL, increasing activity impairments and resulting in more resource use, thus significant unmet medical needs still exist for HCV patients and newer therapies with a favourable side effect profile may have both humanistic and economic benefits. Antiviral therapy is associated with psychiatric side effects and diminished quality of life; patients who developed Major Depressive Disorder as a result of treatment have more severe depressive symptoms, greater impairment on HRQoL, and higher haemoglobin levels than non-depressive patients. Patients often experience moderate anger while undergoing HCV treatment and greater anger is associated with more depression and poorer HRQoL. Treatment history also impacts HRQoL in HCV patients; non-responders have lower HRQoL scores than untreated and relapsed patients.

Fatigue is one of the most important symptoms negatively impacting HRQoL in CHC patients; this impact increases with the degree of liver fibrosis. While changes in HCV disease stage account for some changes in HRQoL, this is a limited explanation; factors such as underlying comorbidities, increasing age, lower income and unattached marital status have a greater negative effect on HRQoL than disease stage.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

As illustrated by Wright et al., 2006[143], HRQoL declines as HCV disease progresses to more advanced disease health states (seeTable 57). Mono-infected patients with non-cirrhotic disease have an average utility of 0.74 at baseline, which increases to 0.79 after treatment for patients that reached SVR. This falls to 0.55 and 0.60 in compensated cirrhosis. In patients with more advanced liver disease such as decompensated cirrhosis, HCC or prior to undergoing liver transplantation utility is even lower (0.45). The Wright et al., 2006[143] utility estimates are consistent with those cited by other economic evaluations, including Grishchenko et al., 2009[138]; Shepherd et al., 2007[139]; Hartwell et al., 2011[135] and Grieve et al., 2006[142].

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. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

HRQL of patients receiving Sofosbuvir therapy was collected in the clinical trials using the following instruments:

- SF-36 (Short Form 36)
- CLDQ-HCV (Chronic Liver Disease Questionnaire – Hepatitis C Virus)
- FACIT-F (Functional Assessment of Chronic Illness Therapy- Fatigue)
- WPAI (Work Productivity and Activity Impairement Questionnaire)

And the data was collected over five time period across the clinical trials:

- Baseline
- Week 12/Early Termination
- 4-Week Post-Treatment
- 12-Week Post-Treatment and
- 24-Week Post-Treatment visits

The SF-36 data was converted to SF-6D utility data and used in the base case. As the NICE reference case recommends EQ-5D, SF-6D data was then mapped to EQ-5D and the latter was included in sensitivity analysis (see section 7.4.4).

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.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.

- Details of validation of the mapping technique.

The SF-36 data was converted to SF-6D using the method proposed by Brazier et al., 2002[181]. The SF-6D utility data was then mapped to EQ-5D using several methodological techniques published in the literature[182-184]. The final mapping was based on the two-part model combining a probit and linear regression models described by Gray et al., 2004[184].

The SF-6D values were used in the base case, rather than the EQ-5D values. This was because the utilities from the SF-6D are more certain due to the well validated conversion method. The EQ-5D utilities are less certain due to the experimental nature of the mapping algorithm used. In the DSA, the ranges for the utility decrements for sofosbuvir were adjusted to include the EQ-5D values.

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.

Details can be found in section **Error! Reference source not found.**.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.

- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

A total of 55 (28 original review and 27 update to the systematic literature review) studies examining different aspects of HRQL in hepatitis C patients were included in the final review. A summary of the characteristics of included publications is provided in section **Error! Reference source not found.**. The SLR of HRQL data was conducted to retrieve articles from 2007 onwards. However, none of the publication identified in this review was deemed more appropriate than two latest UK HTAs (Shepherd et al., 2007[139] and Hartwell et al., 2011[135]). The utility data employed in both studies were based on Wright et al., 2006[143], which are used in our model.

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.

Not applicable as only the utility decrement whilst on treatment with sofosbuvir was obtained from the clinical trials.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

According to the safety analysis presented in section 6.9, there are very low rates of AEs specific to treatment with sofosbuvir. Adverse events resulting from sofosbuvir based regimens are from the inclusion of ribavirin or the combination of pegylated interferon and ribavirin in the regimen. No sofosbuvir specific adverse events are reported.

The impact of any adverse event during sofosbuvir treatment was captured by the mean percentage change in SF-6D value from baseline to the end of treatment. The utility decrements associated with comparators are derived from published literature.

Table 56 Treatment-related utility decrements

Treatment	Utility decrement	Source/Comments
Genotype 1		
Sofosbuvir (IFN eligible; TN)	XXXX	NEUTRINO (SF-6D)
Sofosbuvir (unsuitable for IFN;TN)	XXXX	Assumed equal to NEUTRINO (SF-6D)
PEG-IFN+RBV	-14.8%	Wright et al., 2006[143]; Utility treatment converted from additive (-0.11) to multiplicative by computing the difference between on- and off- treatment divided by the average mild/moderate utility off-treatment
Telaprevir	-14.3%	NICE TA252[146]; Utility treatment converted from additive (-0.102) to multiplicative

Boceprevir	-12.2%	NICE TA253[150]; Utility decrement derived from the literature to reflect the relative reduction that anaemia causes in quality of life during treatment with ribavirin[185]
Genotype 2		
Sofosbuvir (IFN eligible; TN)	XXX	FISSION (SF-6D)
Sofosbuvir (IFN eligible; TE)	XXX	FUSION (SF-6D)
Sofosbuvir (unsuitable for IFN; TN/TE)	XXX	POSITRON (SF-6D)
PEG-IFN+RBV	-14.8%	Wright et al., 2006 (UK mild HCV trial)[143]; Utility treatment converted from additive (-0.11) to multiplicative, by computing the difference between on- and off-treatment divided by the average mild/moderate utility off-treatment
Genotype 3		
SOF+PEG-IFN+RBV (IFN eligible; TN/TE) (12 weeks)	XXX	Assumed equal to NEUTRINO (SF-6D)
SOF+RBV (IFN eligible; TN) (24 weeks)	XXX	FISSION (SF-6D)
SOF+RBV (IFN eligible; TE) (24 weeks)	XXX	FUSION (SF-6D)
Sofosbuvir (unsuitable for IFN; TN/TE)	XXX	POSITRON (SF-6D)
PEG-IFN+RBV	-14.8%	Wright et al., 2006 (UK mild HCV trial)[143]; Utility treatment converted from additive (-0.11) to multiplicative, by computing the difference between on- and off-treatment divided by the average mild/moderate utility off-treatment
Genotype 4/5/6		
Sofosbuvir	XXX	NEUTRINO (SF-6D)
PEG-IFN+RBV	-14.8%	Wright et al., 2006 (UK mild HCV trial)[143]; Utility treatment converted from additive (-0.11) to multiplicative, by computing the difference between on- and off-treatment divided by the average mild/moderate utility off-treatment

IFN, Interferon; NICE, National Institute of Health and Care Excellence; PEG-IFN-2a, Pegylated interferon α - 2a; RBV, Ribavirin; SF-6D, Short Form - 6 Dimensions; TA, Technology Appraisal; TE, Treatment-Experienced; TN, Treatment-naïve

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.

Health state utilities, which are the same across all the indications, are presented in Table 57. Treatment-related utilities were calculated by applying treatment-related utility decrements (section 7.4.8) to the baseline utility estimates.

Estimates were obtained from a systematic literature review presented above. The utilities chosen for the current model were those used by the latest UK HTAs (Hartwell et al., 2011[135]; Shepherd et al., 2007[139]) and were based on the UK trial on mild HCV (Wright et al., 2006[143]).

Table 57 Summary of quality-of-life values

Health-state	Utility	Source	Comments
Baseline – non-cirrhotic	0.74	Wright et al., 2006[143] (UK mild HCV trial)	Average of mild and moderate utilities assuming 77% mild and 23% moderate EQ-5D Publications that used this utility: -Hartwell et al., 2011[135] -Grishchenko et al., 2009[138] -Shepherd et al., 2007[139]
Baseline – compensated cirrhosis	0.55	Wright et al., 2006[143] (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al., 2011[135] -Grishchenko et al., 2009[138]
SVR (utility increment)	0.05	Wright et al., 2006[143] (UK mild HCV trial)	
After treatment at non-cirrhotic stage	0.79	Calculation	Calculated as baseline – non-cirrhotic + utility increment after reaching SVR (0.74 + 0.05)
After treatment at cirrhotic stage	0.60	Calculation	Calculated as baseline – non-cirrhotic + utility increment after reaching SVR (0.55 + 0.05)

Health-state	Utility	Source	Comments
Decompensated cirrhosis	0.45	Wright et al., 2006[143] (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al., 2011[135] -Grishchenko et al., 2009[138] -Shepherd et al., 2007[139]
Hepatocellular carcinoma	0.45	Wright et al., 2006[143] (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al., 2011[135] -Grishchenko et al., 2009[138] -Shepherd et al., 2007[139]
Liver transplant	0.45	Wright et al., 2006[143] (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al., 2011[135] -Shepherd et al., 2007[139]
Post-liver transplant	0.67	Wright et al., 2006[143] (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al., 2011[135]

EQ-5D, EuroQol-5 Dimensions; HCV, Hepatitis C Virus; SVR, Sustained Virological Response; UK, United Kingdom

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[9]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions

[9] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

There was no clinical expert involvement in assessing the utility data for the model.

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?

Liver fibrosis does not occur at the same rate in all individuals, and does not seem to progress linearly, (does not accelerate as more damage occurs). During the non-cirrhotic (non-SVR) health state, patients may feel mild to severe tiredness, jaundice, loss of appetite, nausea and vomiting, soreness where the liver is, fever, increased moodiness and depression or joint pain. As the disease progresses, more signs and symptoms are present. This may include hypertrophic osteoarthropathy, development of ascites and hypogonadism. These complications are due to the decreased functioning of the liver. Further scarring (fibrosis) of the liver results in a progression of chronic HCV to the health state decompensated cirrhosis or can develop into hepatocellular carcinoma. As these health states can be life-threatening, a liver transplant may be an option to decrease the risk of mortality. Liver transplants have risks and complications due to immunosuppressive management needed. These risk and complications contribute to a lower quality of life compared with a healthy person.

The model assumes a decline in QoL when patients progress from non-cirrhotic health states to compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplant. However, an increase in QoL is modelled when patients achieve SVR or after liver transplant (see section 7.4.2). The utility is assumed the same for all patients in any given health state regardless of how long they have been in that state.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded? 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?

According to the safety analysis presented in section 6.9, there is a low rate of AEs specific to treatment with sofosbuvir.

The baseline quality of life assumed in the analysis is defined by the health state in which the patient enters the model.

7.4.13 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The health-related utility of life is assumed constant for as long as the patient remains in one health state and it changes when the patients moves through the different health states. HRQL increases when patients reach SVR and decreases when patients progress to more advanced stages of the disease.

7.4.14 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.

Not applicable

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

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.

Costs used within the model reflect both the third-party payer and societal perspectives, and have four components:

- Treatment costs
- Adverse event costs
- Health state costs
- Monitoring costs

The treatment costs, monitoring costs, health state costs and adverse event costs are reported in detail in section 7.5.5, 7.5.6, and 7.5.7 respectively.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

In this economic analysis, the NHS reference costs, rather than PbR tariffs, were used for the unit costs of managing patients while on treatment. By using them a conservative approach was taken as they reflect the real cost to the service while the PbR tariffs reflect how much the service is reimbursed. In addition, there is a greater level of granularity with reference costs that allows the implementation of a more precise and detailed micro-costing approach. This approach has been adopted to be concordant with previous NICE assessments[135;186].

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. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

Published literature of relevant resource data for the UK was identified through the SLR in section 7.1. A summary table of the studies investigating cost and resource use for treating HCV-related conditions in the UK is presented in appendix **Error! Reference source not found.**.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[10]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Please see section 7.3.5 for a detailed description of the involvement of clinical experts in the development of the economic model.

[10] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

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 of the drugs in the sofosbuvir and comparator regimens are presented in Table 58. Estimates were obtained from British National Formulary (BNF).

Table 58 Treatment unit costs

Drug	Cost per pack	Unit dose*	Quantity/pack	Source	Assumption
SOF	£416.46	400 mg	1	Gilead	
RBV	£246.65	400 mg	56	BNF, June 2013[187]	Copegus® 400mg Tablet. Copegus® was used instead of Rebetol® as it is cheaper, a conservative approach
PEG-IFN-2a	£124.40	180 µg	1	BNF, June 2013[187]	Syringe
Telaprevir	£1,866.50	375 mg	42	BNF, June 2013[187]	
Boceprevir	£2,800.00	200 mg	336	BNF, June 2013[187]	

µg, Microgram; BNF, British National Formulary; mg, Milligram; PEG-IFN-2a, Pegylated interferon α - 2a; RBV, Ribavirin; SOF, Sofosbuvir

*Dose of each unit in a pack

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.

Costs associated with each health state were obtained from a systematic literature review. Estimates are shown in Table 59. These health state costs are independent from the monitoring ones as they are used to cost the monitoring of patients in each health state after treatment. The cost associated with mild and moderate CHC health state are indicated as they were the basis on which the cost of the non-cirrhotic health state was estimated, assuming a 77/23 split between mild and moderate. The assumption was same as that made for the re-estimation of the transition probabilities from non-cirrhosis to cirrhosis.

A table with all the health state costs identified from the systematic literature review and most recent HTAs as potentially suitable for the model is presented in appendix **Error! Reference source not found.**.

Apart from the costs for patients who reached SVR the health state costs chosen for inclusion in the model are from Wright et al. 2006, since these were based on UK studies[143]: The costs for the most advanced stages of the disease are from an observational study on patients recruited from three hepatology centres in London, Newcastle and Southampton; the costs for mild disease were collected from the UK mild hepatitis C RCT[143]; the costs for the liver-transplantation stages were obtained from the national Department of Health-funded liver-transplantation study.[188] These costs were also used by the most recent HTAs (Shepherd et al., 2007[139] and Hartwell et al., 2011[135]). Costs of patients who reached SVR are from Grishchenko et al., 2009[138] because the costs collected from the UK mild hepaticis C RCT (which were used by Shepherd et al., 2007[139] and Hartwell et al., 2011[135]) did not split between non-cirrhotic and cirrhotic patients. All costs have been updated to 2011/2012 costs using the HCHS Pay and Prices Index[189].

Table 59 Health state costs

Health state	**Annual costs**	**Cost year**	**Inflated-values £2011-2012**	**Source**
Non-cirrhotic, mild, NT	£138	2002-2003	£185	Wright et al., 2006[143]
Non-cirrhotic, moderate, NT	£730	2002-2003	£976	Wright et al., 2006[143]
Non-cirrhotic, NT*	-	-	£367	Calculation
Non-cirrhotic, SVR (mild)	£202	2006-2007	£231	Grishchenko et al., 2009[138]
Non-cirrhotic SVR (moderate)	£247	2006-2007	£283	Grishchenko et al., 2009[138]
Non-cirrhotic, SVR*	-	-	£243	
Compensated cirrhosis, NT	£1,138	2002-2003	£1,521	Wright et al., 2006[143]
Compensated cirrhosis, SVR	£437	2006-2007	£500	Grishchenko et al., 2009[138]
Decompensated cirrhosis	£9,120	2002-2003	£12,193	Wright et al., 2006[143]
HCC	£8,127	2002-2003	£10,865	Wright et al., 2006[143]
Liver transplant	£39,470	2002-2003	£52,768	Longworth et al., 2001[188] (also used by Wright et al., 2006[143])
Post-liver transplant				
Follow-up phase (0-12 months)	£9.458	2002-2003	£12,645	Longworth et al., 2001[188](also used by Wright et al., 2006[143])
Follow-up phase (12-24 months)	£1,385	2002-2003	£1,852	Longworth et al., 2001[188](also used by Wright et al., 2006[143])

HCC, Hepatocellular Carcinoma; NT, No Treatment; SVR, Sustained Virological Response

*Weighted average of mild and moderate health state costs/ Patients are followed-up for 2 years.

Monitoring costs refer to the costs of monitoring the patient during treatment with either sofosbuvir or the comparator strategy. These are based on a micro-costing approach. Costs of treatment and treatment-related AEs are not included in any monitoring cost displayed below.

The unit costs used to estimate the monitoring costs are displayed in Table 60. The resource use is taken from the PSSRU unit costs 2012[190] and Shepherd et al., 2007[139] and the costs inflated to 2011-2012 when current costs were unavailable.

Table 60 Resource use unit costs

Item	Unit cost	Cost year	Inflated £2011-2012	Comment	Source
Outpatient appointment					
Gastroenterology - Consultant Led	£140.00	2012-2013	**£140.00**	Sheet name: Total - Outpatient Attendances	National Schedule of Reference Costs Year : 2012-13
Gastroenterology – Non Consultant Led	£107.00	2012-2013	**£107.00**	Sheet name: Total - Outpatient Attendances	National Schedule of Reference Costs Year : 2012-13
Inpatient care (day case)					
Clerking in patient (one hour)	£10.18	2003-2004	**£12.94**		Shepherd et al., 2007[139]
Test and investigations					
Virology					
HCV screen (RNA) = SVR test	£11.33	2003-2004	**£14.40**		Shepherd et al., 2007[139]
HBV	£5.18	2003-2004	**£6.58**		Shepherd et al., 2007[139]
Anti-HIV	£13.50	2012	**£13.50**	Personal communication	External expert opinion
HIV RNA	£35.00	2012	**£35.00**	Personal communication	External expert opinion
Chemical pathology					
Liver function tests	£3.60	2003-2004	**£4.58**		Shepherd et al., 2007[139]
Alfa-fetoprotein	£1.31	2003-2004	**£1.66**		Shepherd et al., 2007[139]
Alfa-Antitrypsin	£5.50	2003-2004	**£6.99**		Shepherd et al., 2007[139]
Thyrotrophic	£3.60	2003-2004	**£4.58**		Shepherd et al., 2007[139]

Free T4	£3.60	2003-2004	**£4.58**		Shepherd et al., 2007[139]
Caeruloplasmin	£6.60	2003-2004	**£8.39**		Shepherd et al., 2007[139]
Iron	£4.30	2003-2004	**£5.46**		Shepherd et al., 2007[139]
Urea and electrolytes	£5.60	2003-2004	**£7.12**		Shepherd et al., 2007[139]
Glucose	£2.50	2003-2004	**£3.18**		Shepherd et al., 2007[139]
Pregnancy test	£0.25	2003-2004	**£0.32**		Shepherd et al., 2007[139]
Thyroid function tests	£13.30	2003-2004	**£16.90**		Shepherd et al., 2007[139]
Alanine aminotransferase	£3.60	2003-2004	**£4.58**		Shepherd et al., 2007[139]
Haematology					
Full blood counT	£2.20	2003-2004	**£2.80**		Shepherd et al., 2007[139]
Ferritin	£10.00	2003-2004	**£12.71**		Shepherd et al., 2007[139]
Blood clotting factors	£2.40	2003-2004	**£3.05**		Shepherd et al., 2007[139]
Blood group	£2.20	2003-2004	**£2.80**		Shepherd et al., 2007[139]
Immunology / chemistry					
Autoantibodies	£22.30	2003-2004	**£28.34**		Shepherd et al., 2007[139]
Immunoglobulins	£2.20	2003-2004	**£2.80**		Shepherd et al., 2007[139]
Cryoglobulin	£11.90	2003-2004	**£15.12**		Shepherd et al., 2007[139]
Radiology					
Ultrasound scan of liver	£48.00	2003-2004	**£61.00**		Shepherd et al., 2007[139]
Chest X-ray	£15.00	2003-2004	**£19.06**		Shepherd et al., 2007[139]
Ultrasound guided biopsy	£173.00	2003-2004	**£219.87**		Shepherd et al., 2007[139]
Ultrasound of liver	£7.20	2003-2004	**£9.15**		Shepherd et al., 2007[139]
ECG	£31.00	2003-2004	**£39.40**		Shepherd et al., 2007[139]

MRI liver	£206.00	2002-2003	**£275.41**	Average of London, Newcastle and Southampton costs	Wright et al., 2006[143]
Molecular pathology					
HCV quantitative viral load	£152.27	2003-2004	**£193.52**		Shepherd et al., 2007[139]
Other tests					
Pulmonary function tests	£1.00	2003-2004	**£1.27**		Shepherd et al., 2007[139]
HCV genotype	£148.00	2003-2004	**£188.09**		Shepherd et al., 2007[139]
Procedures					
Liver biopsy	£126.00	2003-2004	**£160.13**		Shepherd et al., 2007[139]
Fibroscan	£50.00	2008-2009	**£53.50**	Marginal cost. Clinical input suggests that this is likely to be the price charged to the NHS per scan. This is more robust than the Stamuli 2009 estimated cost of £19.52 (range £12.44–33.94)	Stevenson, 2012[191]
Fibrotest	£50.00	2008-2009	**£53.50**	Set similar to the cost of the enhanced liver fibrosis as both are blood tests and are likely to be competitively priced. This estimate is preferred to a value of €90–300 reported by Morra 2007	Stevenson, 2012[191]
Endoscopy diagnosis	£110.00	2002-2003	**£147.06**	Average of London, Newcastle and Southampton costs	Wright et al., 2006[143]

ECG, Electrocardiogram; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; MRI, Magnetic Resonance Imaging; NHS, Food and Drug Administration

Table 61 presents total sums for each of the monitoring phases calculated for the non-cirrhotic and cirrhotic patients.

Table 62 shows the total monitoring costs for each indication, split by non-cirrhotic and cirrhotic. The duration of monitoring corresponds to the average treatment duration which was calculated based on the parameters that have been presented in Table 45 to Table 55. The compilation of all costs used to calculate monitoring costs are shown in **Error! Reference source not found.** to **Error! Reference source not found.**.

Table 61 Monitoring cost summary by treatment phase

Item	Treatment duration	Total cost
Initial evaluation of a new patient with confirmed HCV		
Total non-cirrhotic	-	£623
Total cirrhotic	-	£814
Further investigations for treatment group		
Total non-cirrhotic	-	£467
Total cirrhotic	-	£467
Total non-cirrhotic TE	-	£467
Total cirrhotic TE	-	£467
Monitoring from week 1 to 24 during active treatment: Sofosbuvir cost		
Total non-cirrhotic	4 weeks of treatment	£612
	8 weeks of treatment	£733
	12 weeks of treatment (excl. final visit)	£854
	12 weeks of treatment (incl. final visit)	£1,115
	16 weeks of treatment (excl. final visit)	£976
	16 weeks of treatment (incl. final visit)	£1,237
	24 weeks of treatment	£1,358
Total cirrhotic	4 weeks of treatment	£612
	8 weeks of treatment	£733
	12 weeks of treatment (excl. final visit)	£854
	12 weeks of treatment (incl. final visit)	£1,117
	16 weeks of treatment (excl. final visit)	£976
	16 weeks of treatment (incl. final visit)	£1,239
	24 weeks of treatment	£1,360
Monitoring from week 1 to 24 during active treatment: PEG-IFN comparator		
Total non-cirrhotic	4 weeks of treatment	£719
	8 weeks of treatment	£965
	12 weeks of treatment	£1,314
	16 weeks of treatment	£1,436
	24 weeks of treatment	£1,748
Total cirrhotic	4 weeks of treatment	£719
	8 weeks of treatment	£965
	12 weeks of treatment	£1,437
	16 weeks of treatment	£1,680

	24 weeks of treatment	£2,244
Monitoring from week 1 to 24 during active treatment: Telaprevir/Boceprevir[a]		
Total non-cirrhotic	4 weeks of treatment	£719
	8 weeks of treatment	£965
	12 weeks of treatment	£1,375
	16 weeks of treatment	£1,496
	24 weeks of treatment	£1,869
Total cirrhotic	4 weeks of treatment	£719
	8 weeks of treatment	£965
	12 weeks of treatment	£1,498
	16 weeks of treatment	£1,741
	24 weeks of treatment	£2,366
Monitoring from week 24 to 48 during active treatment: PEG-IFN comparator		
Total non-cirrhotic	28 weeks of treatment	£1,869
	36 weeks of treatment	£2,132
	48 weeks of treatment	£2,566
Total cirrhotic	28 weeks of treatment	£2,366
	36 weeks of treatment	£2,752
	48 weeks of treatment	£3,706
Monitoring from week 24 to 48 during active treatment: Telaprevir/Boceprevir*		
Total non-cirrhotic	28 weeks of treatment	£2,051
	36 weeks of treatment	£2,314
	48 weeks of treatment	£2,809
Total cirrhotic	28 weeks of treatment	£2,548
	36 weeks of treatment	£2,934
	48 weeks of treatment	£3,949
Surveillance of patients who are unsuitable to PEG-IFN		
Total non-cirrhotic	-	£116
Total cirrhotic	-	£355

HCV, Hepatitis C Virus; PEG-IFN, Pegylated interferon α; TE, Treatment-Experienced

[a] 50% of patients have 2 extra visits (assumed in week 9 and 23)

*50% of patients have 2 extra visits (in week 9 and 23) and 50% of patients have 2 extra visits (assumed in week 26 and 47)

Table 62 Monitoring cost summary by indication

Indication	Treatment	Cost, non-cirrhotic	Cost, cirrhotic
Genotype 1			
GT1 TN IFN eligible	SOF+PR	£2,194	£2,386
	Telaprevir+PEG-IFN-2a+RBV	£3,022	£3,767
	Boceprevir+PEG-IFN-2b+RBV	£3,250	£4,080
	PEG-IFN-2a+RBV (48 weeks)	£3,329	£4,402
GT1 TN unsuitable for IFN	SOF+RBV	£2,446	£2,636
	No treatment	£740	£1,168

Indication	Treatment	Cost, non-cirrhotic	Cost, cirrhotic
Genotype 2			
GT2 TN IFN eligible	SOF+RBV	£2,206	£2,398
	PEG-IFN-2a+RBV (24 weeks)	£2,740	£3.353
GT2 TN unsuitable for IFN	SOF+RBV	£2,193	£2,385
	No treatment	£740	£1,168
GT2 TE IFN eligible	SOF+RBV	£1,583	£1,584
	PEG-IFN-2a+RBV (48 weeks)	£2,732	£3,635
	No treatment	£116	£355
GT2 TE unsuitable for IFN	SOF+RBV	£1,487	£1,489
	No treatment	£116	£355
Genotype 3			
GT3 TN IFN eligible	SOF+PR	£1,945	£2,135
	SOF+RBV	£2,443	£2,635
	PEG-IFN-2a+RBV (24 weeks)	£2,699	£3,284
GT3 TN unsuitable for IFN	SOF+RBV	£2,443	£2,635
	No treatment	£740	£1,168
GT3 TE IFN eligible	SOF+PR	£1,251	£1,251
	SOF+RBV	£1,820	£1,821
	PEG-IFN-2a+RBV (48 weeks)	£2,732	£3,635
	No treatment	£116	£355
GT3 TE unsuitable for IFN	SOF+RBV	£1,724	£1,726
	No treatment	£116	£355
Genotype 4/5/6			
GT 4/5/6 TN	SOF+PR	£2,206	£2,398
	PEG-IFN-2a+RBV (48 weeks)	£2,238	£3,121

GT, Genotype; IFN, Interferon; PEG-IFN-2a, Pegylated interferon α - 2a; PEG-IFN-2b, Pegylated interferon α - 2b; PR, Pegylated Interferon α - 2a and Ribavirin; SOF, Sofosbuvir; TE, Treatment-Experienced; TN, Treatment-naïve

*To note, during 2013, data was collected from a single UK centre to measure the patient management costs of triple therapy with protease inhibitors which estimated that management costs could be up to be 6 times higher than that reported in HTA submissions (poster 763 presented at APASL 2014). This suggests that the cost of managing patients with protease inhibitors in clinical practice is significantly higher than the figures being used herein.

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.

Drugs used to treat each adverse event, along with the unit costs of each drug and duration of treatment, are presented in Table 63 and Table 64. Data were obtained from the BNF and National Schedule of Reference Costs. No inpatient costs were considered because most of these AE are treated during outpatient visits, according to expert opinion.[11] Outpatient, GP and specialist costs are shown in Table 65, Table 66 and Table 67, respectively.

Table 63 Adverse event unit costs

Adverse event	Drug	Cost per pack	Unit dose	Quantity/pack	Source
Nausea	Metoclopramide	£1.00	10 mg	28	BNF, June 2013; metoclopramide tablets[187]
Vomiting	Metoclopramide	£1.00	10 mg	28	BNF, June 2013; metoclopramide tablets[187]
Diarrhoea	Loperamide	£0.98	2 mg	30	BNF, June 2013; loperamide caps[187]
Pruritus	Piriton® (chlorphenamine)	£1.62	4 mg	28	BNF, June 2013; Piriton tablets[187]
Anaemia (Epo)	Binocrit® (epoetin alfa)	£50.91	10,000 units	1	BNF, June 2013; Prefilled syringe[187]
Anaemia (blood transfusion)	Blood transfusion	£1,121	NA	1	National Schedule of Reference Costs - Year 2012-13 - NHS trusts and NHS foundation trusts - Elective Inpatient HRG Data
Rash	Hydrocortisone 1% 15g	£1.16	NA	1	BNF, June 2013; Hydrocortisone 1% cream 15g[187]
Thrombocytopenia	Revolade® (eltrombopag)	£1,540.00	50 mg	28	BNF, June 2013[187]
Neutropenia	Neupogen® (filgrastim)	£52.70	600 µg/ml	0.5	BNF, June 2013; Singleject® 0.5-ml prefilled syringe[187]

[11] Janet Catt, Nurse Specialist at the Royal Free Hospital

Adverse event	Drug	Cost per pack	Unit dose	Quantity/pack	Source
Depression	Citalopram	£3.37	20 mg	28	BNF, June 2013[187]; NICE guidance CG91 Depression with a chronic physical health problem[192]

BNF, British National Formulary; CG, Clinical Guidance; EPO, Erythropoietin; HRG, Health Related Group; NA, Not Applicable; NHS, Food and Drug Administration; NICE, National Institute of Health and Care Excellence

Table 64 Adverse event resource use

Adverse event	Drug	Dose	% treated for	Weekly costs	Weeks of treatment	Source
Nausea	Metoclopramide	30 mg/day	100%	£0.75	4	Telaprevir manufacturer's submission[146]
Vomiting	Metoclopramide	30 mg/day	100%	£0.75	4	Telaprevir manufacturer's submission[146]
Diarrhoea	Loperamide	2 mg/day	100%	£0.23	4.3	Telaprevir manufacturer's submission[146]
Pruritus	Piriton® (chlorphenamine)	16 mg/day	100%	£1.62	4	Telaprevir manufacturer's submission[146]
Anaemia (Epo)	Binocrit® (epoetin alfa)	40,000 units/week	1.0%	£204	4	Gao et al., 2012[193]; Assumption: 4-week treatment; % patients treated based on the average of three HCV centres in the UK
Anaemia (blood transfusion)*	Transfusion	1	0.7%	£1,121	NA	Assumption: only one carried out; % patients treated based on the average of three HCV centres in the UK
Rash	Hydrocortisone 1%	NA	100%	£0.29	4	Telaprevir manufacturer's submission[146]
Thrombocytopenia	Revolade® (eltrombopag)	50mg/day	100%	£385	4	BNF, June 2013[187]; Assumption: 4-week treatment
Neutropenia	Neupogen® (filgrastim)	395 µg/d = 5*79	100%	£486	2	BNF, June 2013 (cytotoxic neutropenia) [187]

Depression	Citalopram	20 mg/d	100%	£0.84	4	BNF, June 2013[187]; Assumption: 4-week treatment

BNF, British National Formulary; EPO, Erythropoietin; HCV, Hepatitis C Virus; NA, Not Applicable; UK, United Kingdom

*HRG "Single Plasma Exchange, Leucophoresis or Red Cell Exchange, with length of stay 2 days or less, 19 years and over"

Table 65 Other adverse event costs – outpatient costs

Adverse event	**% patients with outpatient stays**	**Number of outpatient visits**	**Cost per outpatient visit**	**Total Cost**	**Source[12]**
Outpatient costs (treatment of each adverse event)					
Nausea	0%	0	£0.00	£0.00	Expert Opinion
Vomiting	0%	0	£0.00	£0.00	Expert Opinion
Diarrhoea	0%	0	£0.00	£0.00	Expert Opinion
Pruritus	0%	0	£0.00	£0.00	Expert Opinion
Anaemia (Epo)	100%	6	£58.00	£3.48	Expert Opinion; PSSRU unit costs 2012 - Hospital, day ward
Anaemia (blood transfusion)*	NA	NA	NA	NA	Assumed to be included in the HRG cost
Rash	100%	4	£58.00	£232.00	Expert Opinion; PSSRU unit costs 2012 - Hospital, day ward
Thrombocytopenia	100%	6	£58.00	£348.00	Expert Opinion; PSSRU unit costs 2012 - Hospital, day ward
Neutropenia	100%	6	£58.00	£348.00	Expert Opinion; PSSRU unit costs 2012 - Hospital, day ward
Depression	0%	0	£0.00	£0.00	Expert Opinion

EPO, Erythropoietin; PSSRU, Personal Social Services Research Unit

*HRG "Single Plasma Exchange, Leucophoresis or Red Cell Exchange, with length of stay 2 days or less, 19 years and over"

[12] Janet Catt, Nurse Specialist at the Royal Free Hospital

Table 66 Other adverse event costs – GP costs

Adverse event	% patients visiting GPs	Number of GP visits	Cost per GP visit	Total Cost	Source[13]
GP costs (treatment of each adverse event)					
Nausea	0%	0	£0.00	£0.00	Expert Opinion
Vomiting	0%	0	£0.00	£0.00	Expert Opinion
Diarrhoea	0%	0	£0.00	£0.00	Expert opinion
Pruritus	0%	0	£0.00	£0.00	Expert opinion
Anaemia (Epo)	0%	0	£0.00	£0.00	Expert opinion
Anaemia (blood transfusion)*	0%	0	£0.00	£0.00	Expert opinion
Rash	0%	0	£0.00	£0.00	Expert opinion
Thrombocytopenia	0%	0	£0.00	£0.00	Expert opinion
Neutropenia	0%	0	£0.00	£0.00	Expert opinion
Depression	100%	8	£19.33	£154.67	Expert opinion ; PSSRU unit costs 2012 - Registrar group

EPO, Erythropoietin; GP, General Practitioner; PSSRU, Personal Social Services Research Unit

Table 67 Other adverse event costs – specialist costs

Adverse event	% patients visiting specialist	Number of specialist visits	Cost per specialist visit	Total Cost	Source
Specialist costs (treatment of each adverse event)					
Nausea	0%	0	£0.00	£0.00	Expert opinion
Vomiting	0%	0	£0.00	£0.00	Expert opinion
Diarrhoea	0%	0	£0.00	£0.00	Expert opinion
Pruritus	0%	0	£0.00	£0.00	Expert opinion
Anaemia (Epo)	50%	1	£215	£1.08	Expert opinion; National Schedule of Reference Costs Year 2012-13 - Consultant-led costs for Hepatology

[13] Janet Catt, Nurse Specialist at the Royal Free Hospital

Anaemia (blood transfusion)*	50%	1	£215	£0.75	Expert opinion; National Schedule of Reference Costs Year 2012-13 - Consultant-led costs for Hepatology
Rash	100%	2	£215	£430.00	Expert opinion; National Schedule of Reference Costs Year 2012-13 - Consultant-led costs for Hepatology
Thrombocytopenia	50%	1	£215	£107.50	Expert opinion; National Schedule of Reference Costs Year 2012-13 - Consultant-led costs for Hepatology
Neutropenia	50%	1	£215	£107.50	Expert opinion; National Schedule of Reference Costs Year 2012-13 - Consultant-led costs for Hepatology
Depression	0%	0	£0.00	£0.00	Assumption

EPO, Erythropoietin

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*

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

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.

The uncertainties around structural assumptions in the baseline were tested in a deterministic sensitivity analysis. Both one-way and multi-way sensitivity analyses were used. The inputs that were tested in the sensitivity analysis include the proportion of cirrhotic and non-cirrhotic patients, SVR rates, incidence of adverse events, treatment costs, costs of health states, utilities, discount rates, and a number of different transition probabilities (see section 7.6.2). This approach has been adopted to be concordant with previous NICE assessments[135;186]

One-way sensitivity analysis was used for the majority of the inputs. Listed below are the groups of inputs that were tested simultaneously in the sensitivity analysis:

- The incidence of all adverse events, apart from anaemia treated with EPO and blood transfusion (which were varied individually). This was done separately for sofosbuvir and the comparator

- The costs of non-cirrhotic and cirrhotic disease after treatment, HCC, liver transplant and post-liver transplant

- Utility values for HCC, liver transplant and post-liver transplant
- Transition probabilities from compensated cirrhosis to HCC, from HCC, liver transplant and post-liver transplant to death and from HCC to liver transplant
- Discounting of costs and outcomes
- Probability of death

Structural sensitivity analysis was also included by including the possibility of recurrence or re-infection for both non-cirrhotic and cirrhotic patients that reach SVR.

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.

The model varies individual inputs to identify model drivers and analyse areas of uncertainty within the model. These variations of inputs and their rationale are listed below for the inputs that are common to all indications. For the indication-specific inputs this information is presented in appendix **Error! Reference source not found.**.

Table 68 Deterministic sensitivity analysis general inputs

Variable	Base case	Minimum	Maximum	Rationale
Treatment Costs				
Cost per pack of sofosbuvir	£417	£313	£521	Assumption
Costs				
Non-cirrhotic disease SVR - monitoring (2 years)	£243	£182	£303	Between 0% and +25%
Non-cirrhotic disease SVR - no monitoring	£243	£0.00	£0.00	Between 0% and +25%
Cirrhotic disease - SVR	£500	£282	£779	Based on the 95% CI of the distribution used for the PSA
Decompensated cirrhosis	£12,193	£8,541	£16,485	Based on the 95% CI of the distribution used for the PSA
Health state costs (off treatment)				
Non-cirrhotic disease - no treatment	£367	£170	£637	Based on the 95% CI of the distribution used for the PSA
Cirrhotic disease - no treatment	£1,521	£992	£2,162	Based on the 95% CI of the distribution used for the PSA
Hepatocellular carcinoma	£10,865	£6,451	£16,412	Based on the 95% CI of the distribution used for the PSA

Variable	Base case	Minimum	Maximum	Rationale
Liver transplant	£52,768	£39,576	£65,960	Between 0% and +25%
Post-liver transplant Year 1	£12,645	£9,483	£15,806	Between 0% and +25%
Post-liver transplant Year 2	£1,851	£1,388	£2,315	Between 0% and +25%
Utilities (non-treatment specific)				
Non-cirrhotic - without treatment	0.74	0.71	0.77	Based on the 95% CI of the distribution used for the PSA
Cirrhotic - without treatment	0.55	0.44	0.65	Based on the 95% CI of the distribution used for the PSA
SVR - Utility increment	0.05	0.002	0.17	Based on the 95% CI of the distribution used for the PSA
Decompensated cirrhosis	0.45	0.39	0.51	Based on the 95% CI of the distribution used for the PSA
Hepatocellular carcinoma	0.45	0.39	0.51	Based on the 95% CI of the distribution used for the PSA
Liver transplant	0.45	0.39	0.51	Based on the 95% CI of the distribution used for the PSA
Post-liver transplant	0.67	0.61	0.73	Based on the 95% CI of the distribution used for the PSA
Transition probabilities (non-treatment specific)				
From non-cirrhotic SVR to non-cirrhotic (recurrence)	-	-	0.01	External expert opinion
From cirrhotic SVR to cirrhotic (recurrence)	-	-	0.01	External expert opinion
From non-cirrhotic SVR to non-cirrhotic (re-infection)	-	-	0.01	External expert opinion
From cirrhotic SVR to cirrhotic (re-infection)	-	-	0.01	External expert opinion
From compensated cirrhosis to decompensated cirrhosis	0.04	0.02	0.06	Based on the 95% CI of the distribution used for the PSA
From decompensated cirrhosis to HCC	0.01	0.00	0.04	Based on the 95% CI of the distribution used for the PSA
From decompensated cirrhosis to liver transplant	0.03	0.01	0.06	Based on the 95% CI of the distribution used for the PSA

Variable	Base case	Minimum	Maximum	Rationale
From decompensated cirrhosis to death	0.13	0.11	0.15	Based on the 95% CI of the distribution used for the PSA
From compensated cirrhosis to HCC	0.01	0.00	0.04	Based on the 95% CI of the distribution used for the PSA
From HCC to death	0.43	0.37	0.49	Based on the 95% CI of the distribution used for the PSA
From liver transplant to death	0.21	0.13	0.31	Based on the 95% CI of the distribution used for the PSA
From post-liver transplant to death	0.06	0.04	0.08	Based on the 95% CI of the distribution used for the PSA
HCC to Liver transplant	-	-	0.01	External expert opinion
Discounting				
Outcomes	3.5%	0.0%	6.0%	NICE
Costs	3.5%	0.0%	6.0%	NICE
Probability of death by age				
15-24	0.000300	0.000225	0.000375	Assumption: +/-25%
25-34	0.000525	0.000394	0.000656	Assumption: +/-25%
35-44	0.001174	0.000881	0.001468	Assumption: +/-25%
45-54	0.002622	0.001966	0.003277	Assumption: +/-25%
55-64	0.006479	0.004859	0.008099	Assumption: +/-25%
65-74	0.016561	0.012421	0.020702	Assumption: +/-25%
75-84	0.047676	0.035757	0.059595	Assumption: +/-25%
85 and over	0.135540	0.101655	0.169425	Assumption: +/-25%

CI, Confidence Interval; HCC, Hepatocellular Carcinoma; PSA, Probabilistic Sensitivity Analysis; SVR, Sustained Virological Response

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).

A PSA was undertaken to characterise uncertainty in input parameters, propagate the uncertainty through the model and to present the implications of parameter uncertainty. The model parameters tested in this PSA that are common to all the indications are listed in Table 69 along with the distributions used to test these parameters. The same information in presented in appendix for the indication-specific parameters varied in the PSA (appendix **Error! Reference source not found.**).For the analysis, 1000 simulations were performed.

Table 69 Probabilistic sensitivity analysis general inputs

Parameter	Distribution and parameters	Expected Value	Comments
Quality of life			
On PEG-IFN+RBV (mono-infected)	Gamma, α=8 β=0	-14.8%	
On Telaprevir	Gamma, α=204 β=0	-14.3%	
On Boceprevir	Gamma, α=143 β=0	-12.2%	
Non-cirrhotic			
Baseline quality of life (mono-infected)	Beta, α=707 β=248	0.74	
Compensated cirrhosis			
Baseline quality of life (mono-infected)	Beta, α=47 β=39	0.55	
SVR			
Quality of life (utility increment for mono-infected)	Gamma, α=1.25 β=0.04	0.05	
Other health states			
Mono-infected			
Decompensated cirrhosis	Beta, α=124 β=151	0.45	
Hepatocellular carcinoma	Beta, α=124 β=151	0.45	
Liver transplant	Beta, α=124 β=151	0.45	
Post-liver transplant	Beta, α=163 β=80	0.67	
Costs			
Non-cirrhotic disease			
No treatment	Gamma, α=9 β=39	£367	Average of mild and moderate from Wright et al. 2006[143] inflated, assuming 0.77 mild and 0.23 moderate
SVR	Gamma, α=25 β=10	£243	Average of mild and moderate from Grishchenko et al. 2009[138] inflated, assuming 0.77 mild and 0.23 moderate
Cirrhotic disease			
No treatment	Gamma, α=26 β=59	£1,521	
SVR	Gamma, α=15 β=33	£500	
Other health states			
Decompensated cirrhosis	Gamma, α=36 β=338	£12,193	
Hepatocellular carcinoma	Gamma, α=18 β=600	£10,865	
Liver Transplant			
Waiting list phase	Gamma, α=15 β=324	£4,983	

Assessment phase	Gamma, α=15 β=732	£11,248	
Transplant stage	Gamma, α=90 β=407	£36,538	
Post liver transplant (follow-up 0-12 months)	Gamma, α=14 β=918	£12,645	
Post liver transplant (follow-up 0-24 months)	Gamma, α=15 β=122	£1,852	
Cost per pack			
Sofosbuvir	Uniform, α=313 β=521	£416	
RBV	Uniform, α=222 β=271	£247	
PEG-IFN-2a	Uniform, α=112 β=137	£124	
Telaprevir	Uniform, α=1680 β=2053	£1,867	
Boceprevir	Uniform, α=2520 β=3080	£2,800	
Transition probabilities (mono-infected)			
GT1			
From non-cirrhotic to compensated cirrhosis - age 30 years	Beta, α=9 β=1481	0.006	Running a Markov model based mild->moderate and moderate->cirrhosis TPS from Grishchenko 2009[138]
From non-cirrhotic to compensated cirrhosis - age 40 years	Beta, α=11 β=1088	0.01	Running a Markov model based mild->moderate and moderate->cirrhosis TPS from Grishchenko 2009[138]
From non-cirrhotic to compensated cirrhosis - age 50 years	Beta, α=10 β=619	0.016	Running a Markov model based mild->moderate and moderate->cirrhosis TPS from Grishchenko 2009[138]
Non-GT1			
From non-cirrhotic to compensated cirrhosis - age 30 years	Beta, α=20 β=2209	0.009	Running a Markov model based mild -> moderate and moderate -> cirrhosis TPS from Grishchenko 2009[138]
From non-cirrhotic to compensated cirrhosis - age 40 years	Beta, α=21 β=1511	0.014	Running a Markov model based mild -> moderate and moderate -> cirrhosis TPS from Grishchenko 2009[138]
From non-cirrhotic to compensated cirrhosis - age 50 years	Beta, α=8 β=316	0.025	Running a Markov model based mild -> moderate and moderate -> cirrhosis TPS from Grishchenko 2009[138]
Other			
From compensated cirrhosis to decompensated cirrhosis	Beta, α=15 β=360	0.039	

From compensated cirrhosis to HCC	Beta, α=2 β=136	0.014	
From decompensated cirrhosis to HCC	Beta, α=2 β=136	0.014	
From decompensated cirrhosis to liver transplant	Beta, α=7 β=211	0.03	
From decompensated cirrhosis to death	Beta, α=147 β=984	0.13	
From HCC to death	Beta, α=117 β=155	0.43	
From LT to death	Beta, α=16 β=61	0.21	
From Post-LT to death	Beta, α=23 β=379	0.057	

GT, Genotype; HCC, Hepatocellular Carcinoma; PEG-IFN, Pegylated interferon α; PEG-IFN-2a, Pegylated interferon α - 2a; RBV, Ribavirin; SVR, Sustained Virological Response; TP, Transition Probability

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

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.

The proportion of patients reaching SVR as predicted by the model are very similar to the corresponding outcomes reported from clinical trials. Tables summarising the SVR rates obtained from the clinical trials and predicted by the model for each comparator by indication are presented in appendix (section **Error! Reference source not found.**).

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.

The Markov traces showing the number of patients in the cohort in each health state over time are presented in appendix (section **Error! Reference source not found.** to **Error! Reference source not found.**). For all indications the Markov trace indicates that patients receiving sofosbuvir therapy spend more time in the SVR health state compared with the other treatments.

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 cycle are accrued by multiplying the number of patients in each health state by the utility for that state and applying discounting. To calculate the ICER, QALYs are then summed across the time horizon of the analysis. Patient Markov traces, showing QALYs accrued in the cohort in each health state over time, are provided in appendix **Error! Reference source not found.** for the indications and regimens.

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 are presented in the tables below for each treatment regimen for each genotype. Costs, LYs and QALYs have been discounted at a rate of 3.5% and assumed a time horizon of patients reaching 100 years of age.

Across all genotypes and patient populations while the total discounted cost per patient receiving sofosbuvir treatment is higher than with the comparator regimen, significant improvements in health outcomes are noted, with reductions in long-term complications, such as DCC, HCC, LT, and mortality.

Genotype 1 treatment-naïve Interferon eligible

Table 70 Model outputs by clinical outcome for GT1 TN IFN eligible

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000 pt	DCC /10,000 pt	HCC /10,000 pt	Liver transplant /10,000pt	Deaths /10,000 pt
SOF+PEG-IFN-2a+RBV (12 wks)	£44,123	15	20	206	318	136	46	9,527
PEG-IFN-2a+RBV (48 wks)	£24,994	14	19	1,369	1,483	635	213	9,623
Telaprevir+PE	£38,835	15	20	604	711	305	103	9,559

G-IFN-2a+RBV								
Boceprevir+PEG-IFN-2a+RBV	£39,221	14	20	883	912	390	131	9,577

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; PEG-IFN-2a, Pegylated interferon α - 2a; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 1 treatment-naïve unsuitable for interferon

Table 71 Model outputs by clinical outcome for GT1 TN unsuitable for IFN

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+RBV (24 wks)	£84,129	14	20	779	888	380	128	9574
No treatment	£20,225	13	19	2446	2229	953	319	9690

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 2 treatment-naïve interferon eligible

Table 72 Model outputs by clinical outcome for GT2 TN IFN eligible

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+RBV (12 wks)	£42,271	16	22	118	223	96	34	9,522
PEG-IFN-2a+RBV (24 wks)	£14,492	16	21	661	757	325	112	9,565

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 2 treatment-naïve unsuitable for interferon

Table 73 Model outputs by clinical outcome for GT2 TN unsuitable for IFN

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+RBV (12 wks)	£41,477	15	20	215	153	65	21	9,515
No treatment	£21,426	13	19	3,230	2,520	1,077	359	9,718

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 2 treatment-experienced interferon eligible

Table 74 Model outputs by clinical outcome for GT2 TE IFN eligible

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+RBV (12 wks)	£42,269	15	20	277	320	137	46	9,528
No treatment	£20,771	13	19	3,230	2,520	1,077	359	9,718
PEG-IFN-2a+RBV (48 wks)	£24,022	14	19	2,087	1,626	694	230	9,641

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; PEG-IFN-2a, Pegylated interferon α - 2a; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 2 treatment-experienced unsuitable for interferon

Table 75 Model outputs by clinical outcome for GT2 TE unsuitable for IFN

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+RBV (12 wks)	£41,468	15	20	262	205	87	29	9,519
No treatment	£20,771	13	19	3,230	2,520	1,077	359	9,718

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 3 treatment-naïve interferon eligible

Table 76 Model outputs by clinical outcome for GT3 TN IFN eligible: SOF+PEG-IFN-2a+RBV

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+PEG-IFN-2a+RBV (12 wks)	£44,674	16	21	85	301	130	46	9,527
PEG-IFN-2a+RBV (24 wks)	£19,704	15	20	949	1,535	661	231	9,623

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; PEG-IFN-2a, Pegylated interferon α - 2a; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 3 treatment-naïve unsuitable for interferon

Table 77 Model outputs by clinical outcome for GT3 TN unsuitable for IFN

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+RBV (24 wks)	£78,543	15	20	197	201	86	29	9,518
No treatment	£23,406	12	18	2,990	2,786	1,193	402	9,736

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 3 treatment-experienced interferon eligible

Table 78 Model outputs by clinical outcome for GT3 TE IFN eligible: SOF+PEG-IFN-2a+RBV

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+PEG-IFN-2a+RBV (12 wks)	£42,374	15	20	505	471	201	67	9,541
No treatment	£22,740	12	18	2,990	2,786	1,193	402	9,736
PEG-IFN-2a+RBV (48 wks)	£25,531	13	19	1,933	1,801	770	258	9,652

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; PEG-IFN-2a, Pegylated interferon α - 2a; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 3 treatment-experienced unsuitable for interferon

Table 79 Model outputs by clinical outcome for GT3 TE unsuitable for IFN

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+RBV (24 wks)	£81,568	14	20	452	796	342	117	9,564
No treatment	£22,740	12	18	2,990	2,786	1,193	402	9,736

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 4/5/6 treatment-naïve

Table 80 Model outputs by clinical outcome for GT4/5/6 TN

Outcome	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+PEG-	£46,573	15	20	0	657	283	100	9,549

IFN-2a+RBV (12 wks)								
PEG-IFN-2a+RBV (48 wks)	£22,631	14	19	1,185	1,305	558	188	9,608

CC, Compensated Cirrhosis; DCC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; LY, Life Year; PEG-IFN-2a, Pegylated interferon α - 2a; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

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 cost category. Suggested formats are presented below.

The disaggregated incremental QALYs and costs by health state and predicted resource use are shown in appendix **Error! Reference source not found.** for each genotype and comparison.

Across all genotypes a higher number of QALYs are gained with the sofosbuvir regimen. This is explained by the fact that more patients are cured with sofosbuvir (that is, more patients reach the SVR health state which is associated with increased utility values), and consequently fewer patients progress to the more severe health state where HRQoL is expected to decrease. This highlights the overall positive impact of sofosbuvir on patient's quality of life.

Patients treated with sofosbuvir have lower costs associated with off- treatment health states compared with those in the comparator arms. This is a consequence of better efficacy of sofosbuvir, which means that fewer patients will suffer from more advanced health states and AEs. Total costs are however higher in the sofosbuvir arm due to higher drug costs.

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.

Sofosbuvir-based regimens offer a favourable cost-effectiveness profile compared with current standards of care. Across all HCV genotypes (GT1–6), including patients with compensated cirrhosis, and irrespective of treatment experience or IFN eligibility, sofosbuvir is associated with overall QoL gains (QALYs), a greater probability of cure (SVR rates), and reduction in end stage liver disease and death. The ICERs for sofosbuvir regimen against each comparator are summarised as below and detailed in Table 81.

Genotype 1

- For patients with GT1 infection, triple therapy with SOF + PEG-IFN-2a + RBV for 12 weeks offers a simple, efficacious, well tolerated treatment which is cost-effective compared with all currently available treatments (ICERs <£15,000/QALY, Table 81)

- In addition, for those GT1 patients who are unsuitable for IFN-based therapy and currently have no treatment options available, SOF + RBV for 24 weeks

offers the potential of a cure using an all oral, IFN-free regimen (ICER: £49,249/QALY, Table 81)

Genotype 2

- SOF + RBV for 12 weeks is highly cost-effective (ICERs <£13,000/QALY, Table 81) against current available comparators among GT2 patients who are either TN or TE unsuitable for IFN and TE IFN eligible

- Although for IFN eligible GT2 TN patients, SOF + RBV for 12 weeks has an estimated ICER of £46,324/QALY (Table 81) as compared to PEG-IFN-2a + RBV, SOF + RBV has an SVR rate of 95% in this population, thus representing a substantial improvement in efficacy and the chance for cure.

Genotype 3

- In GT3 patients, triple therapy with SOF + PEG-IFN-2a + RBV for 12 weeks offers a cost-effective option for the treatment of IFN eligible TN and TE patients (ICERs: <£21,000/QALY, Table 81)

- In addition, for those TN or TE GT3 patients who are unsuitable for IFN-based therapy and currently have no treatment options available, an all oral, IFN-free regimen of SOF + RBV for 24 weeks offers the potential of a cure using a cost-effective IFN-free regimen (ICERs <£29,000/QALY, Table 81)

Genotype 4/5/6

- The ICER for SOF + PEG-IFN-2a + RBV for 12 weeks compared with PEG-IFN-2a + RBV is estimated to be £26,797/QALY (Table 81) in patients with GT 4/5/6 infection. This ICER is considered to be conservative since the SVR for cirrhotic patients (50%) is based on a small number of patients. The SVR rate for non-cirrhotic patients treated with a sofosbuvir-based regimen is 100%

Table 81 Summary of base-case cost-effectiveness results (ICER for sofosbuvir against each comparator: £/QALY)

Indication	Sofosbuvir regimen	Comparator			
		No treatment	PEG-IFN-2a+RBV	Telaprevir+ PEG-IFN-2a+RBV	Boceprevir +PEG-IFN-2b+RBV
GT1					
TN IFN eligible	SOF+PEG-IFN-2a+RBV (12 wks)	-	£14,930	£11,836	£7,292
TN unsuitable for IFN	SOF+RBV (24 wks)	£49,249	-	-	-
GT2					
TN IFN eligible	SOF+RBV (12 wks)	-	£46,324	-	-
TN unsuitable for IFN		£8,154	-	-	-
TE IFN eligible		£9,274	£12,519	-	-
TE unsuitable for IFN		£8,591	-	-	-
GT3					
TN IFN eligible	SOF+PEG-IFN-2a+RBV (12 wks)	-	£20,613	-	-
TN unsuitable	SOF+RBV 24	£21,478	-	-	-

Indication	Sofosbuvir regimen	Comparator			
		No treatment	PEG-IFN-2a+RBV	Telaprevir+ PEG-IFN-2a+RBV	Boceprevir +PEG-IFN-2b+RBV
for IFN	(wks)				
TE IFN eligible	SOF+PEG-IFN-2a+RBV (12 wks)	£8,557	£12,246	-	-
TE unsuitable for IFN	SOF+RBV (24 wks)	£28,569	-	-	-
GT4/5/6					
TN	SOF+PEG-IFN-2a/RBV (12 wks)	-	£26,797	-	-

GT, Genotype; IFN, Interferon; PEG-IFN-2a, Pegylated interferon α - 2a; PEG-IFN-2b, Pegylated interferon α - 2b; RBV, Ribavirin; SOF, Sofosbuvir; TE, Treatment-Experienced; TN, Treatment-naïve; wk, Week

Additionally, the ICERs for each treatment against the least expensive comparator (ICER versus baseline) are presented in the following tables for each indication, as well as the incremental analysis ranking technologies in terms of dominance and extended dominance (ICER incremental).

Genotype 1 treatment-naïve interferon eligible

Table 82 Cost-effectiveness results, GT1 TN IFN eligible

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
PEG-IFN-2a+RBV (48 wks)	£24,994	19.3	13.8	NA	NA	NA	NA	NA
Telaprevir+PEG-IFN-2a+RBV	£38,835	19.9	14.6	£13,841	0.6	0.8	£16,587	Extended dominance
Boceprevir+PEG-IFN-2b+RBV	£39,221	19.8	14.4	£14,227	0.4	0.6	£23,360	Dominated
SOF+PEG-IFN-2a+RBV (12 wks)	£44,123	20.2	15.1	£19,129	0.9	1.3	£14,930	£14,930

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; PEG-IFN-2a, Pegylated interferon α - 2a; PEG-IFN-2b, Pegylated interferon α - 2b; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 1 treatment-naïve unsuitable for interferon

Table 83 Cost-effectiveness results, GT1 TN unsuitable for IFN

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
No treatment	£20,225	18.7	13.0	NA	NA	NA	NA	NA
SOF+RBV (24 wks)	£84,129	19.5	14.3	£63,903	0.8	1.3	£49,249	£49,249

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 2 treatment-naïve interferon eligible

Table 84 Cost-effectiveness results, GT2 TN IFN eligible

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
PEG-IFN-2a+RBV (24 wks)	£14,492	21.1	15.6	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£42,271	21.6	16.2	£27,779	0.5	0.6	£46,324	£46,324

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 2 treatment-naïve unsuitable for interferon

Table 85 Cost-effectiveness results, GT2 TN unsuitable for IFN

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
No treatment	£21,426	18.6	12.8	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£41,477	20.4	15.3	£20,051	1.8	2.5	£8,154	£8,154

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 2 treatment-experienced interferon eligible

Table 86 Cost-effectiveness results, GT2 TE IFN eligible

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
No treatment	£20,771	18.6	12.8	NA	NA	NA	NA	NA
PEG-IFN-2a+RBV (48 wks)	£24,022	19.3	13.7	£3,251	0.7	0.9	£3,778	£3,778
SOF+RBV (12 wks)	£42,269	20.2	15.1	£21,498	1.6	2.3	£9,274	£12,519

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; PEG-IFN-2a, Pegylated interferon α - 2a; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 2 treatment-experienced unsuitable for interferon

Table 87 Cost-effectiveness results, GT2 TE unsuitable for IFN

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
No treatment	£20,771	18.6	12.8	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£41,468	20.3	15.2	£20,697	1.7	2.4	£8,591	£8,591

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 3 treatment-naïve interferon eligible

Table 88 Cost-effectiveness results, GT3 TN IFN eligible, SOF+PEG-IFN-2a+RBV

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
PEG-IFN-2a+RBV (24 wks)	£19,704	20.3	14.7	NA	NA	NA	NA	NA
SOF+PEG-IFN-2a+RBV (12 wks)	£44,674	21.5	15.9	£24,970	1.2	1.2	£20,613	£20,613

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; PEG-IFN-2a, Pegylated interferon α - 2a; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 3 treatment-naïve unsuitable for interferon

Table 89 Cost-effectiveness results, GT3 TN unsuitable for IFN

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
No treatment	£23,406	18.3	12.4	NA	NA	NA	NA	NA
SOF+RBV (24 wks)	£78,543	20.3	15.0	£55,137	2.1	2.6	£21,478	£21,478

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 3 treatment-experienced interferon eligible

Table 90 Cost-effectiveness results, GT3 TE IFN, SOF+PEG-IFN+RBV

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
No treatment	£22,740	18.3	12.4	NA	NA	NA	NA	NA
PEG-IFN-2a+RBV (48 wks)	£25,531	19.1	13.4	£2,791	0.9	0.9	£3,037	£3,037
SOF+PEG-IFN-2a+RBV (12 wks)	£42,374	20.1	14.7	£19,634	1.9	2.3	£8,557	£12,246

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; PEG-IFN-2a, Pegylated interferon α - 2a; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 3 treatment-experienced unsuitable for interferon

Table 91 Cost-effectiveness results, GT3 TE unsuitable for IFN

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
No treatment	£22,740	18.3	12.4	NA	NA	NA	NA	NA
SOF+RBV (24 wks)	£81,568	19.8	14.5	£58,828	1.5	2.1	£28,569	£28,569

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

Genotype 4/5/6 treatment-naïve

Table 92 Cost-effectiveness results, GT4/5/6 TN

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
PEG-IFN-2a+RBV (48 wks)	£22,631	19.5	13.9	NA	NA	NA	NA	NA
SOF+PEG-IFN-2a+RBV (12 wks)	£46,573	19.8	14.8	£23,942	0.3	0.9	£26,797	£26,797

ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; PEG-IFN-2a, Pegylated interferon α - 2a; QALY, Quality-Adjusted Life Year; RBV, Ribavirin; SOF, Sofosbuvir; wk, Week

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 was varied relative to its base case value. The method adopted and the parameters tested were described in section 7.6.2.

Patient characteristics, treatment efficacy (SVR), adverse event rates, costs, utilities, transition probabilities, discounting rates, and the rate of mortality were all tested in a sensitivity analysis, and the change in ICER measured. The size of the change was then ranked and the top 24 inputs which affected the base case ICER the most were listed below for each genotype and intervention/comparator comparison.

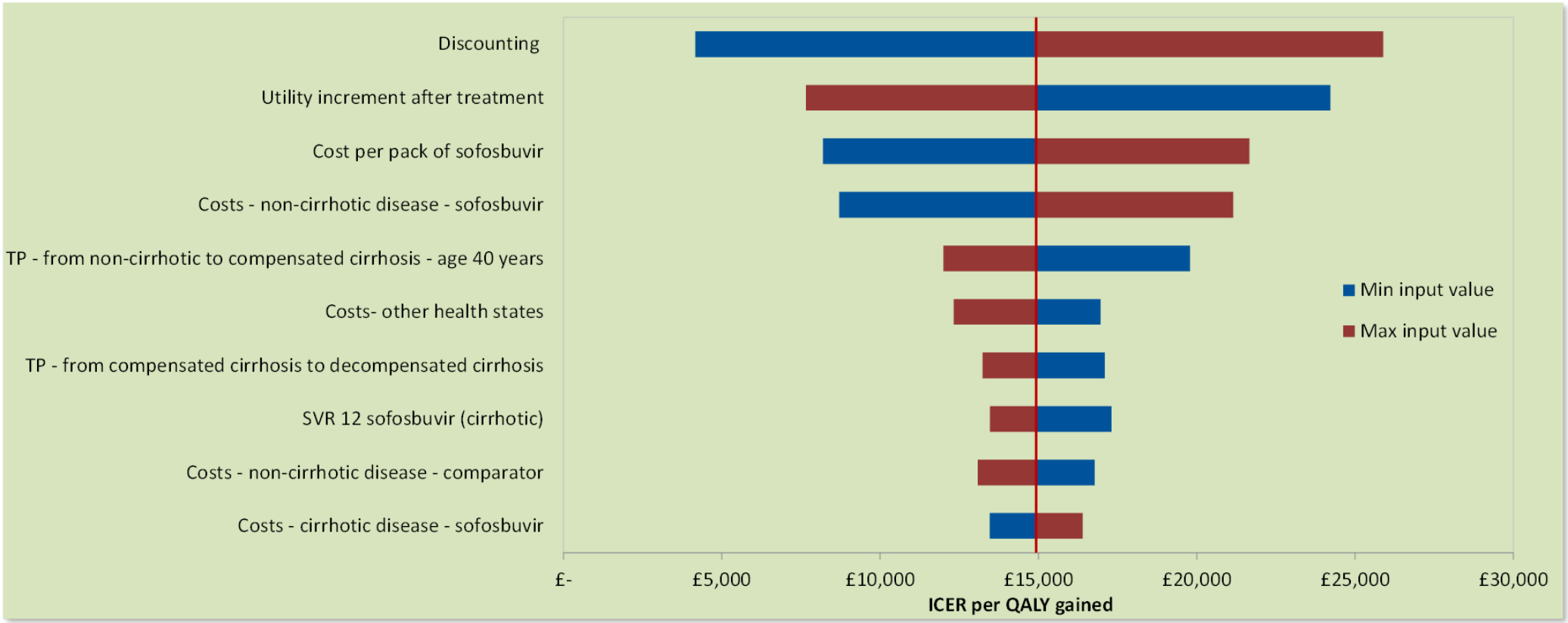
Please note that the sensitivity analysis results using the SVRs obtained from the meta-analysis have been included in appendix for reference only (section 10.14.10). The results for the alternative treatment of SOF + RBV for 24 weeks in GT3 patients are presented in appendix **Error! Reference source not found.**.

Genotype 1 treatment-naïve interferon eligible

SOF + PEG-IFN-2a + RBV (12 weeks) versus PEG-IFN-2a + RBV (48 weeks)

For a time horizon of 100 years, the base case ICER per QALY gained for SOF + PEG-IFN + RBV (12 weeks) compared with PEG-IFN + RBV (48 weeks is £14,930/QALY (Table 81). The tornado chart is shown in Figure 21. Discounting (varied between 0% and 6% for costs and outcomes simultaneously) and utility increment after reaching SVR (varied between 0.002 and 0.17) have the greatest impact. Nevertheless, the ICER/QALY did not go beyond £26,000/QALY.

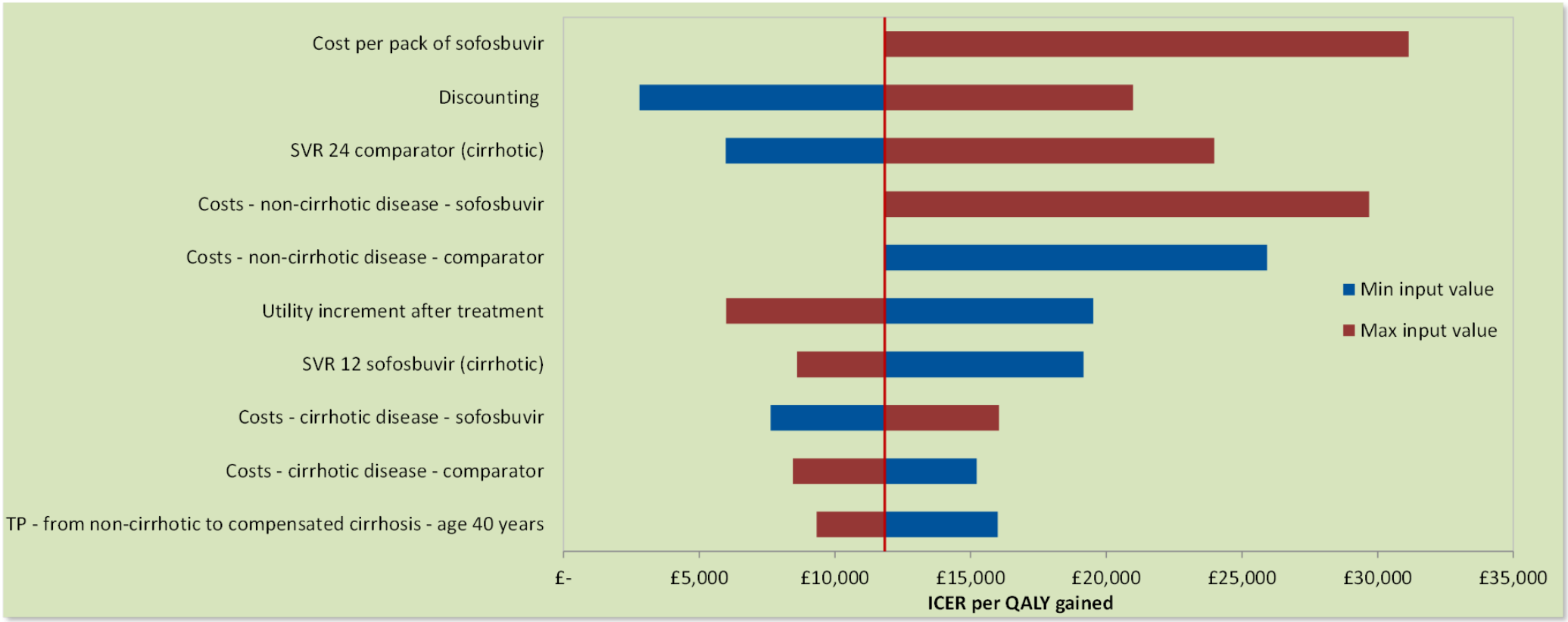
Figure 21 Tornado diagram for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT1 TN IFN eligible



SOF + PEG-IFN-2a + RBV (12 weeks) versus Telaprevir + PEG-IFN-2a + RBV

For a time horizon of 100 years, the base case ICER per QALY gained for SOF + PEG-IFN + RBV (12 weeks) compared with PEG-IFN + RBV (48 weeks) is £11,836/QALY (Table 81). The tornado chart is shown in Figure 22. The sensitivity analyses for SOF + PEG-IFN-2a + RBV (12 weeks) compared with telaprevir+ PEG-IFN–2a+ RBV show that by varying some parameters, sofosbuvir can become the dominant strategy (i.e. being both less expensive and more efficacious) or be cost-effective with ICERs estimated in the majority to be below £32,000 per QALY gained. Discounting (varied between 0% and 6% for costs and outcomes simultaneously) and the SVR rate for cirrhotic patients on telaprevir (varied between 40.8% and 80.9%) are found to have the biggest impact on the results.

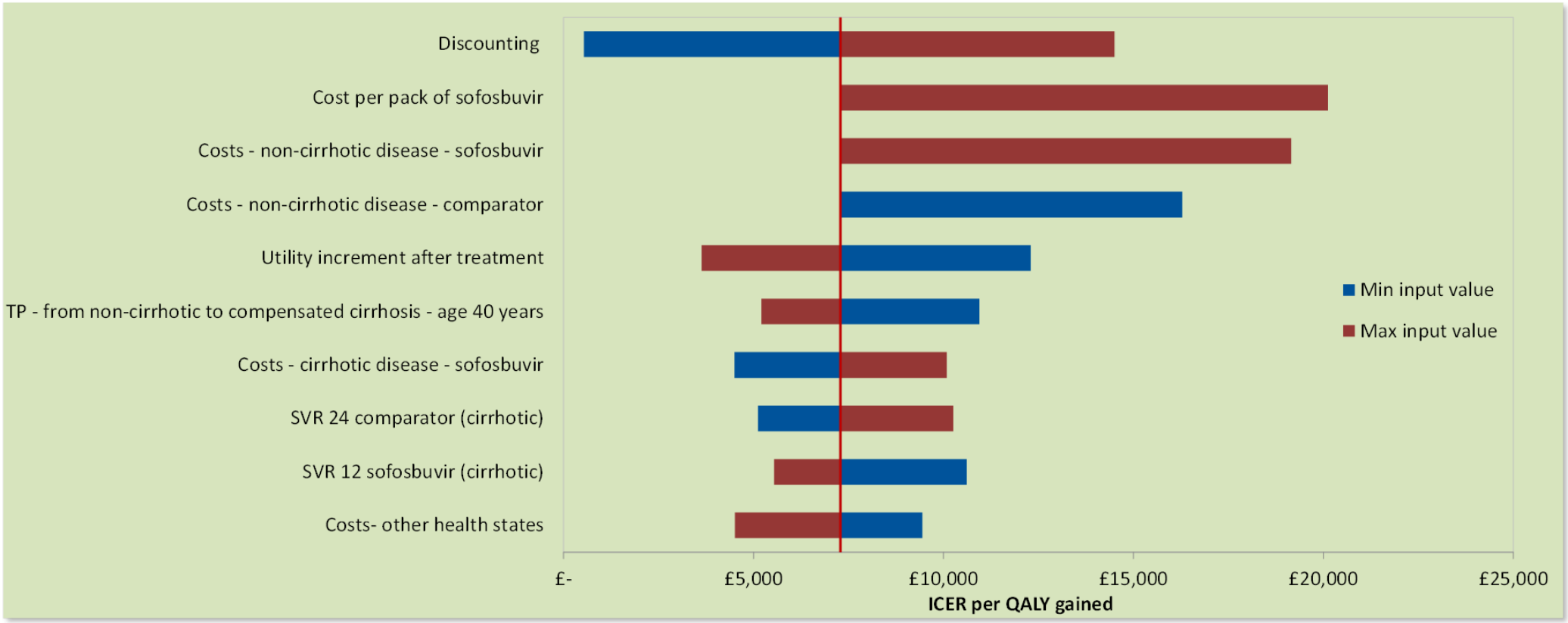
Figure 22 Tornado diagram for SOF+PEG-IFN-2a+RBV (12 weeks) versus TPV+PEG-IFN-2a+RBV in GT1 TN IFN eligible



SOF + PEG-IFN-2a + RBV (12 weeks) versus Boceprevir + PEG-IFN-2b + RBV

For a time horizon of 100 years, the base case ICER per QALY gained for SOF + PEG-IFN + RBV (12 weeks) compared with PEG-IFN + RBV (48 weeks is £7,292/QALY (Table 81). All the sensitivity analyses conducted show that SOF + PEG-IFN+ RBV (12 weeks), when compared to boceprevir + PEG-IFN-2b + RBV, is either dominant or results in ICERs lower than £21,000/QALY. The tornado chart is shown in Figure 23. The parameter which impacts the ICER the most is discounting (varied between 0% and 6% for costs and outcomes simultaneously).

Figure 23 Tornado diagram for SOF+PEG-IFN+RBV (12 weeks) versus BOC+PEG-IFN-2b+RBV (48 weeks) in GT1 TN IFN eligible

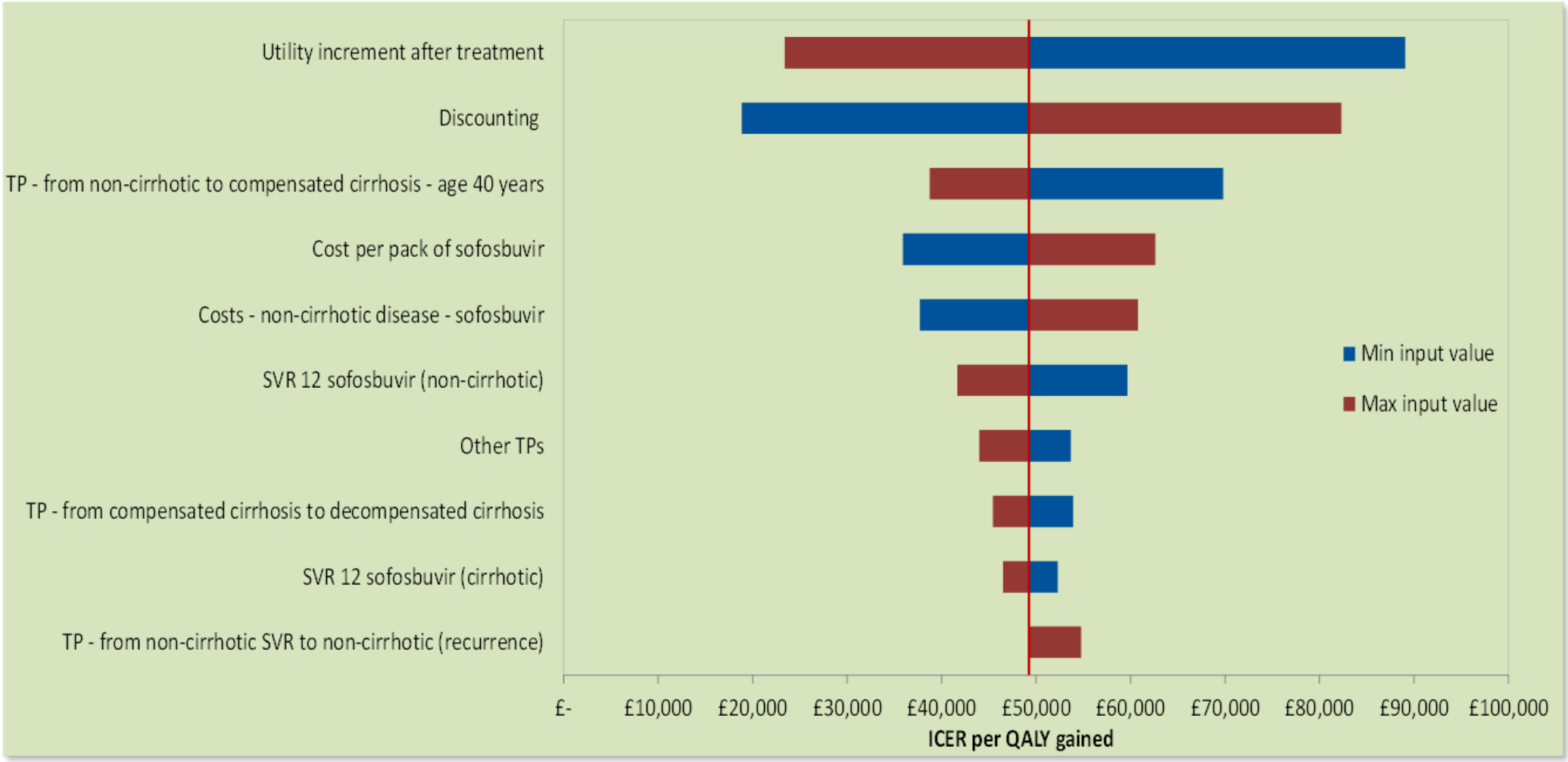


Genotype 1 treatment-naïve unsuitable for interferon

SOF + RBV (24 weeks) versus No treatment

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir and RBV (24 weeks) compared with no treatment is shown to be £49,249/QALY (Table 81). The tornado chart is shown in Figure 24. Utility increment after reaching SVR (varied between 0.002 and 0.17) and discounting (varied between 0% and 6% for costs and outcomes simultaneously) have the greatest impact, with a difference between the minimum and maximum ICER of £65,674/QALY for the utility increments after reaching SVR and £63,451/QALY for discounting.

Figure 24 Tornado diagram for SOF+RBV (24 weeks) versus NT in GT1 TN unsuitable for IFN

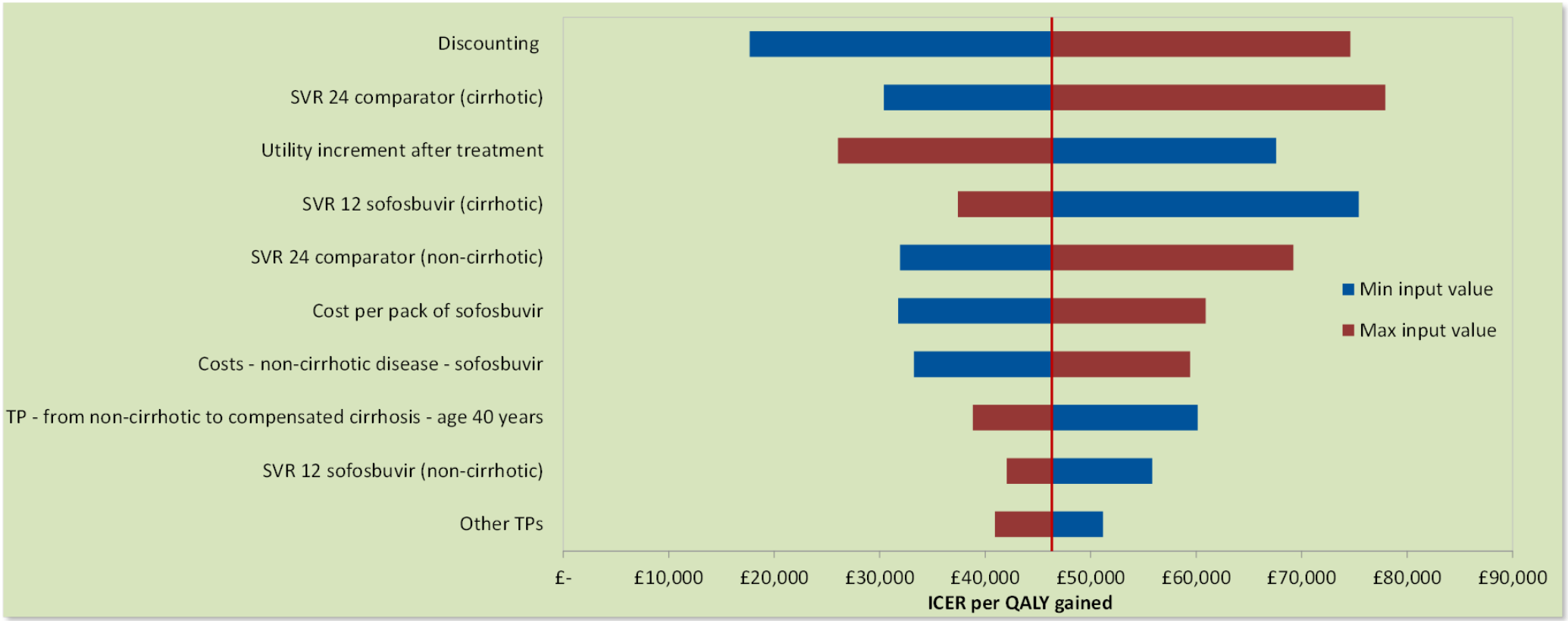


Genotype 2 treatment-naïve interferon eligible

SOF + RBV (12 weeks) versus PEG-IFN-2a + RBV (24 weeks)

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir and RBV (12 weeks) compared with PEG-IFN and RBV (24 weeks) is shown to be £46,324/QALY (Table 81). The tornado chart is shown in Figure 25. Discounting (varied between 0% and 6% for costs and outcomes simultaneously), the SVR for cirrhotic patients on PEG-IFN and RBV (varied between 34.9% and 84.8%) and the utility increment utility increment after reaching SVR (varied between 0.002 and 0.17) have the greatest impact, with a difference between the minimum and maximum ICERs over £40,000/QALY.

Figure 25 Tornado diagram for SOF+RBV (12 weeks) versus PEG-IFN-2a+RBV (24 weeks) in GT2 TN IFN eligible

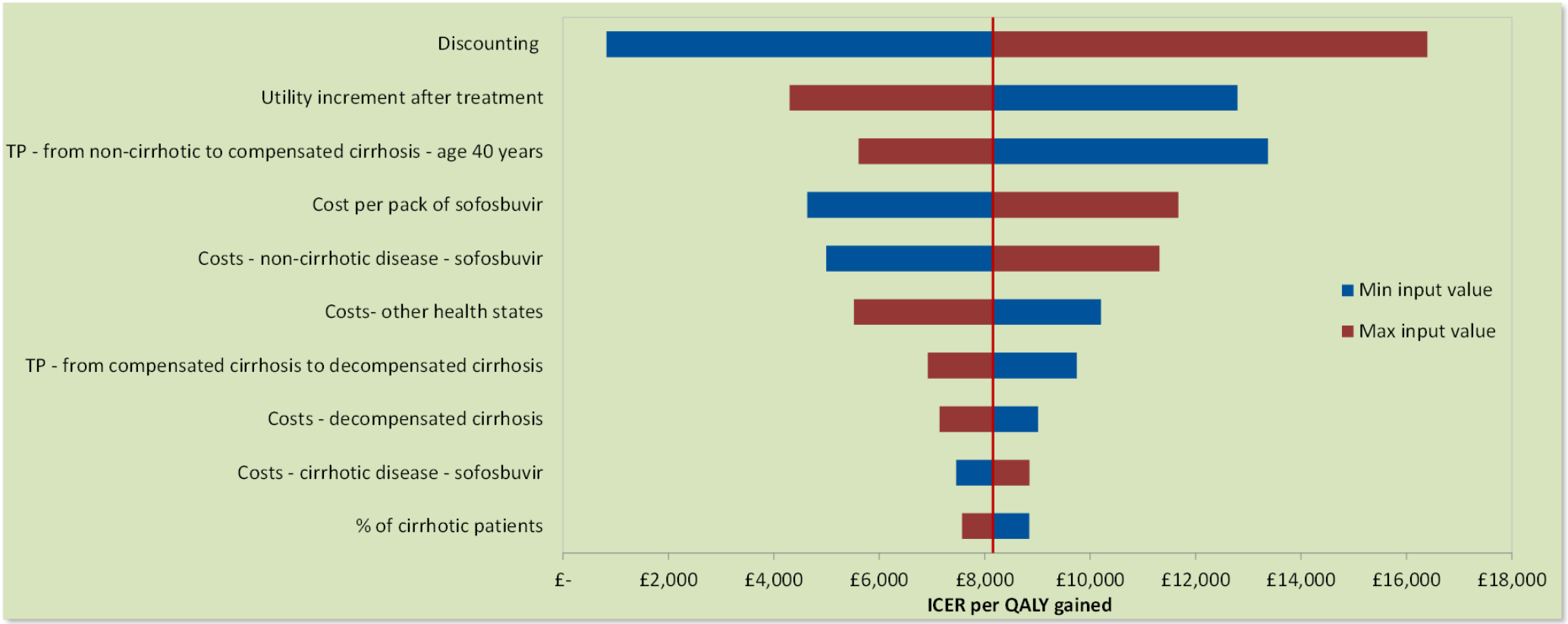


Genotype 2 treatment-naïve unsuitable for interferon

SOF + RBV (12 weeks) versus No treatment

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir and RBV (12 weeks) compared with no treatment is shown to be £8,154/QALY (Table 81). The tornado chart is shown in Figure 26. Discounting (varied between 0% and 6% for costs and outcomes simultaneously) has the greatest impact on the results and originates the highest ICER, although still below £20,000/QALY.

Figure 26 Tornado diagram for SOF+RBV (12 weeks) versus NT in GT2 TN unsuitable for IFN

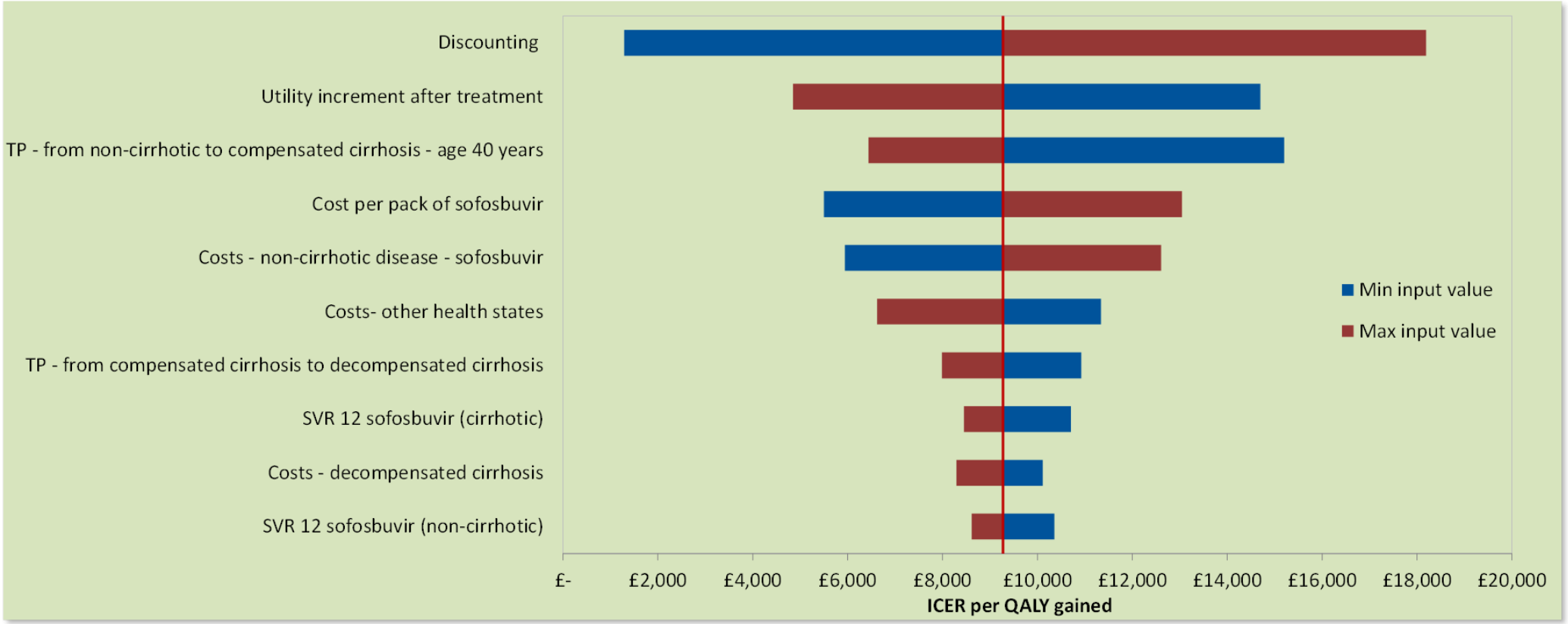


Genotype 2 treatment-experienced interferon eligible

SOF + RBV (12 weeks) versus No treatment

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir and RBV (12 weeks) compared with no treatment was shown to be £9,274/QALY (Table 81). The tornado chart is shown in Figure 27. Discounting (varied between 0% and 6% for costs and outcomes simultaneously), the utility increment after reaching SVR (varied between 0.002 and 0.17) and the TP from non-cirrhotic to compensated cirrhosis for patients between 40 and 50 years of age (varied between 0.004 and 0.025) have the greatest impact, although the ICERs continue to be below £20,000/QALY.

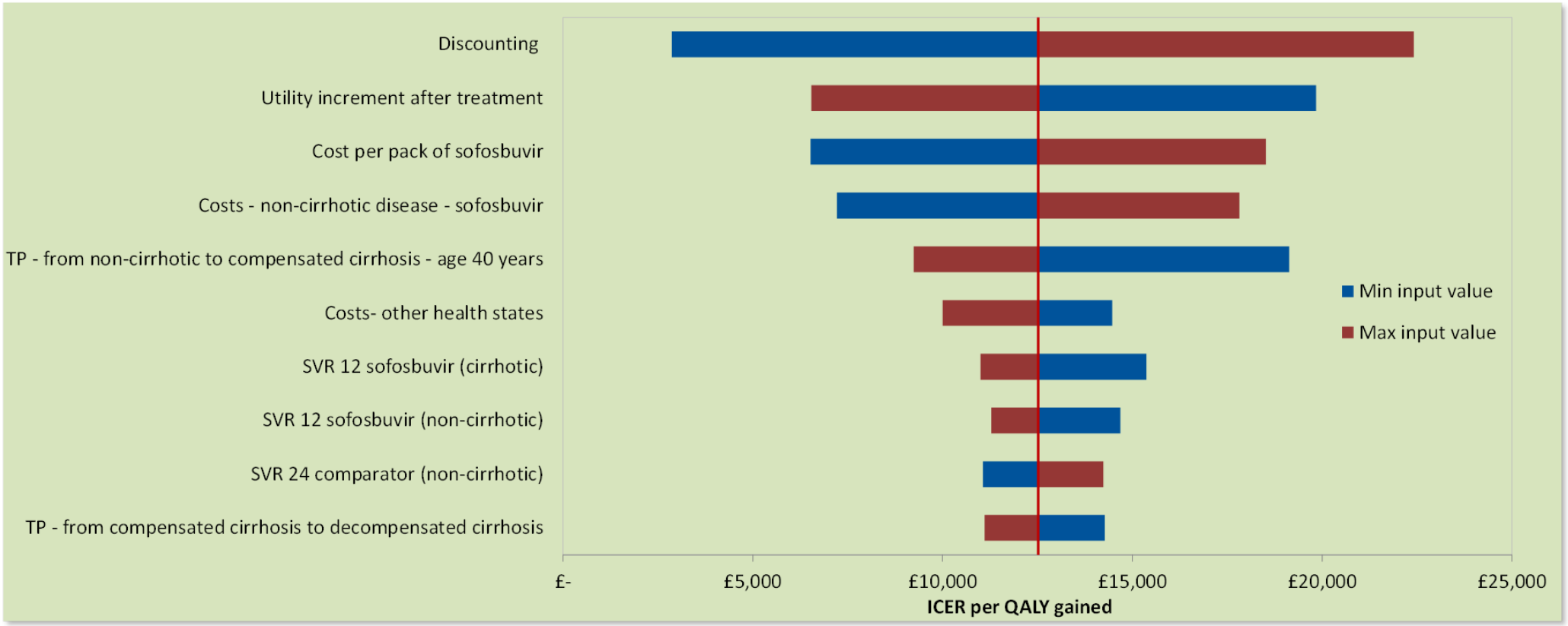
Figure 27 Tornado diagram for SOF+RBV (12 weeks) versus NT GT2 TE IFN eligible



SOF + RBV (12 weeks) versus PEG-IFN-2a + RBV (48 weeks)

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir and RBV (12 weeks) compared with PEG-IFN and RBV (48 weeks) was shown to be £12,519/QALY (Table 81). The tornado chart is shown in Figure 28. Discounting (varied between 0% and 6% for costs and outcomes simultaneously) and the utility increment after reaching SVR (varied between 0.002 and 0.17) have the greatest impact. Nevertheless, except for a value of 6% for the discount rates for costs and outcomes, all ICERs are below £20,000/QALY.

Figure 28 Tornado diagram for SOF+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT2 TE IFN eligible

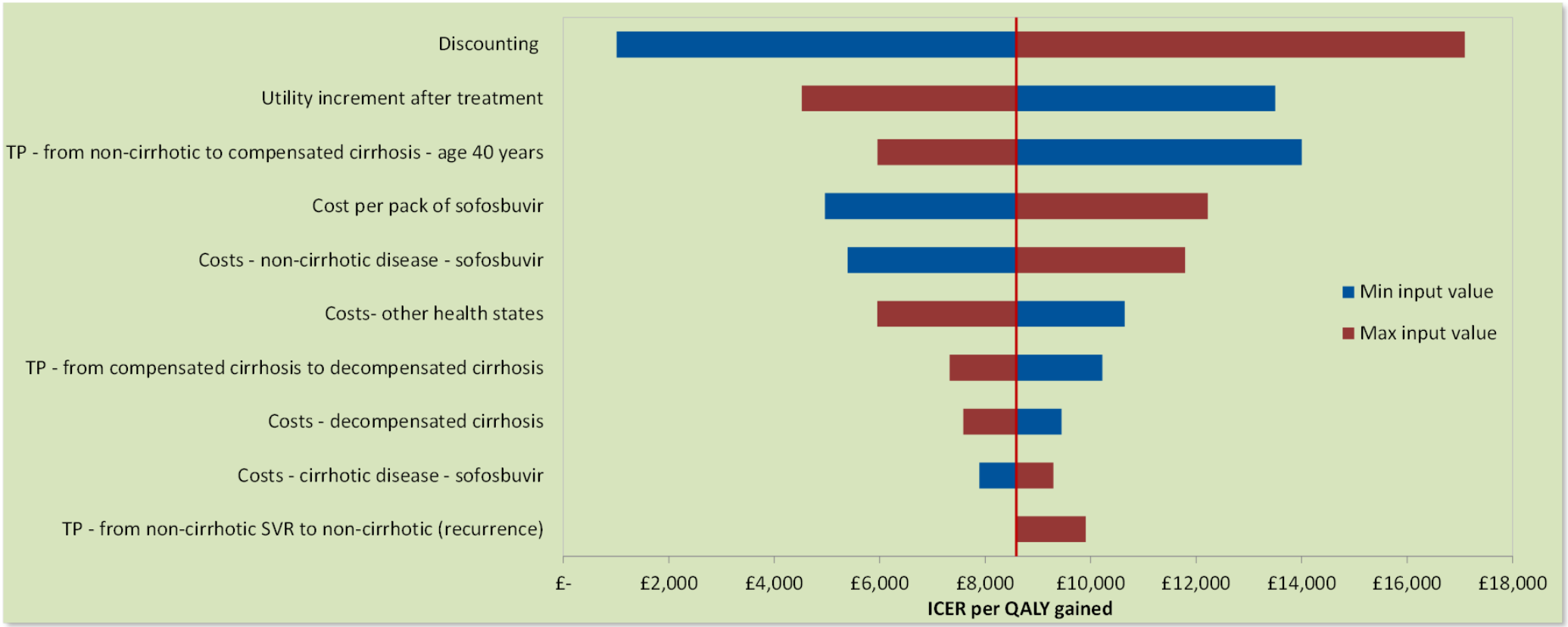


Genotype 2 treatment-experienced unsuitable for interferon

SOF + RBV (12 weeks) versus No treatment

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir and RBV (12 weeks) compared with no treatment is shown to be £8,591/QALY (Table 81). The tornado chart is shown in Figure 29. Discounting (varied between 0% and 6% for costs and outcomes simultaneously), the utility increment after reaching SVR (varied between 0.002 and 0.17) and the TP from non-cirrhotic to compensated cirrhosis for patients between 40 and 50 years of age (varied between 0.004 and 0.025) have the greatest impact, although the ICERs continue to be below £20,000/QALY.

Figure 29 Tornado diagram for SOF+RBV (12 weeks) versus NT in GT2 TE unsuitable for IFN

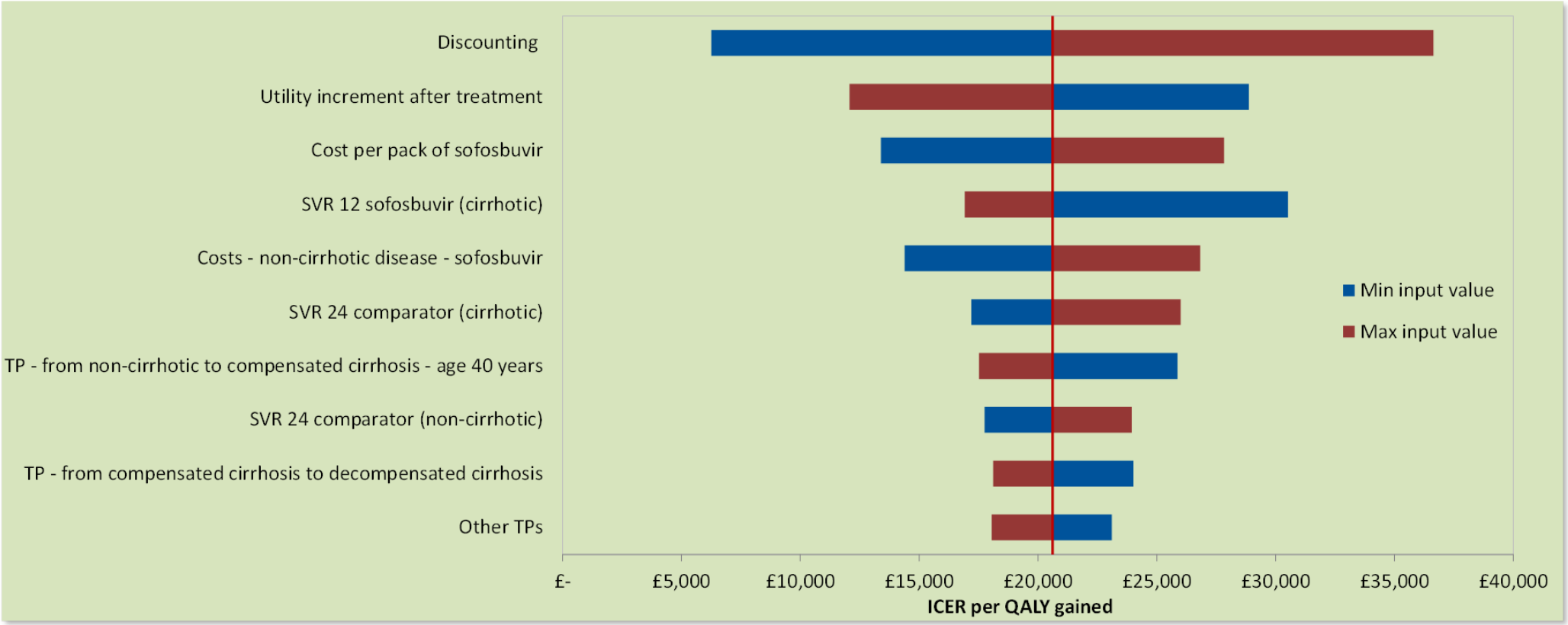


Genotype 3 treatment-naïve interferon eligible

SOF + PEG-IFN-2a + RBV (12 weeks) versus PEG-IFN-2a + RBV (24 weeks)

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir, PEG-IFN and RBV (12 weeks) compared with PEG-IFN and RBV (24 weeks) is shown to be £20,613/QALY (Table 81). The tornado chart is shown in Figure 30. Discounting rates (varied between 0% and 6% for costs and outcomes simultaneously) have the greatest impact originating ICERs just over £30,000/QALY.

Figure 30 Tornado diagram for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (24 weeks) in GT3 TN IFN



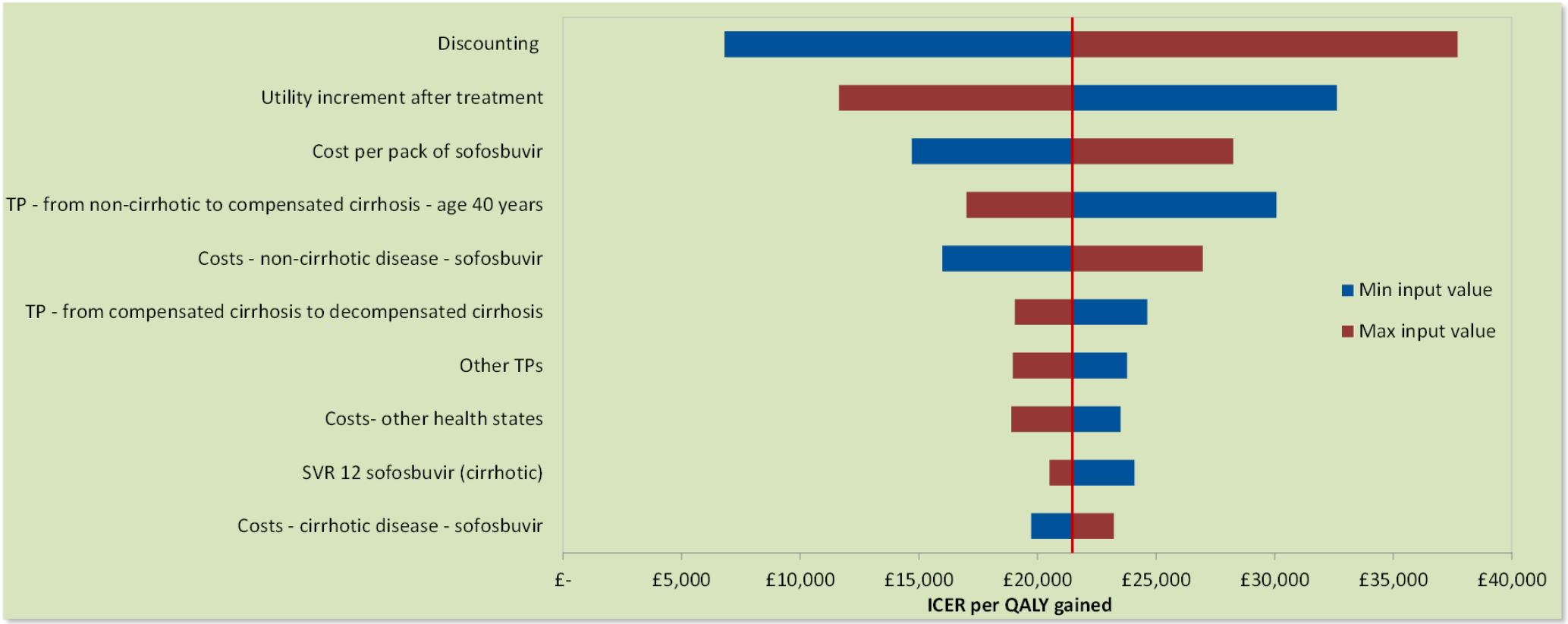
Note: The results for SOF + RBV for 24 weeks are presented in appendix (section **Error! Reference source not found.**).

Genotype 3 treatment-naïve unsuitable for interferon

SOF + RBV (24 weeks) versus No treatment

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir and RBV (24 weeks) compared with no treatment is shown to be £21,478/QALY (Table 81). The tornado chart is shown in Figure 31. Discount rates (varied between 0% and 6% for costs and outcomes simultaneously) have the greatest impact originating ICERs just over £30,000/QALY.

Figure 31 Tornado diagram for SOF+RBV (24 weeks) versus NT in GT3 TN unsuitable for IFN

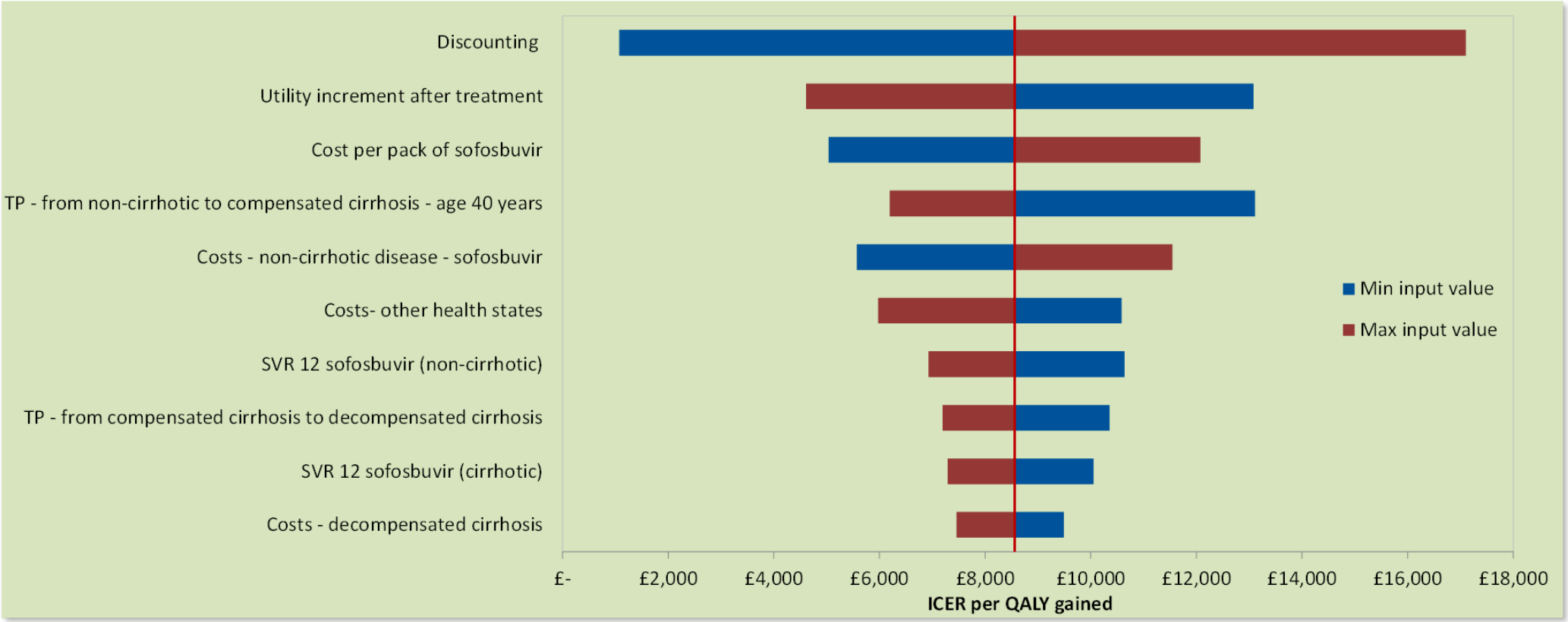


Genotype 3 treatment-experienced interferon eligible

SOF + PEG-IFN-2a + RBV (12 weeks) versus No treatment

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir, PEG-IFN and RBV (12 weeks) compared with no treatment is shown to be £8,557/QALY (Table 81). The tornado chart is shown in Figure 32. Discounting (varied between 0% and 6% for costs and outcomes simultaneously) and the utility increment after reaching SVR (varied between 0.002 and 0.17) have the greatest impact, although ICERs all remain < £20,000/QALY.

Figure 32 Tornado diagrams for SOF+PEG-IFN-2a+RBV (12 weeks) versus NT in GT3 TE IFN eligible

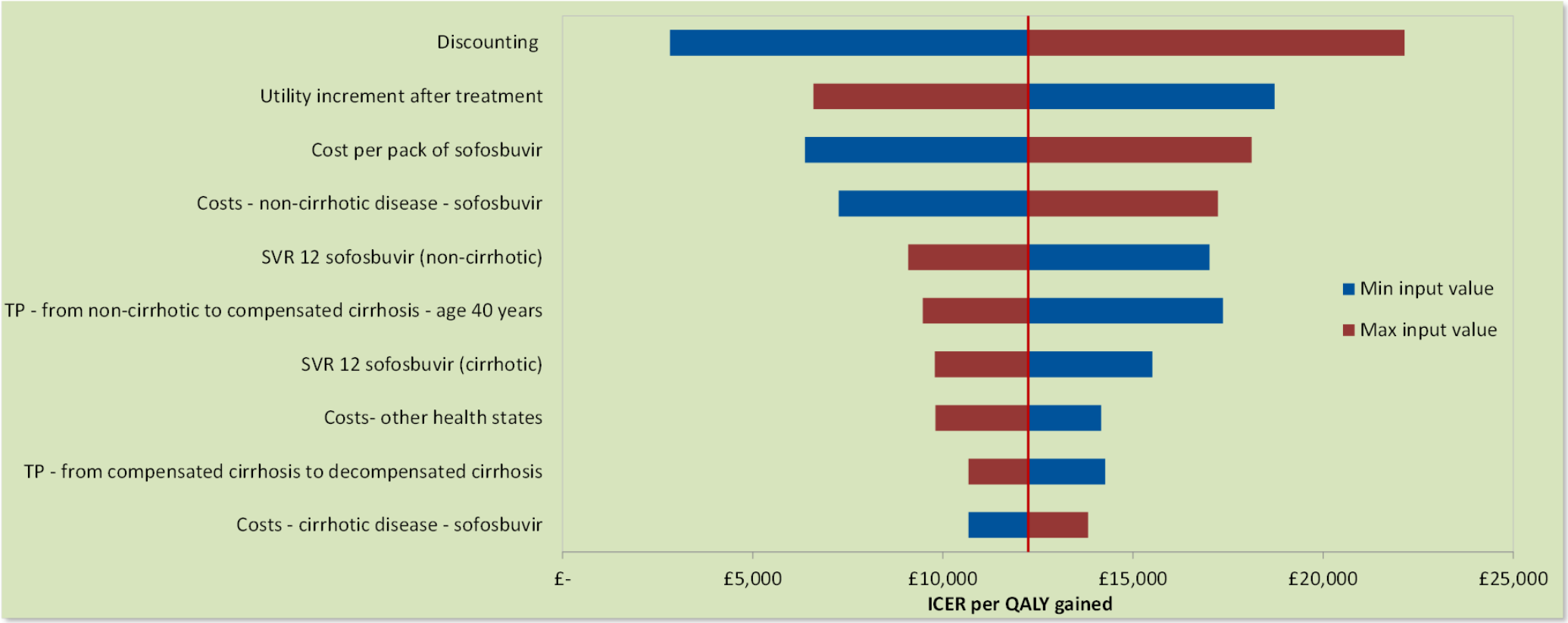


Note: The results for SOF + RBV for 24 weeks are presented in appendix (section **Error! Reference source not found.**).

SOF + PEG-IFN-2a + RBV (12 weeks) versus PEG-IFN-2a + RBV (48 weeks)

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir, PEG-IFN and RBV (12 weeks) compared with PEG-IFN and RBV (48 weeks) is shown to be £12,246/QALY (Table 81). The tornado chart is shown in Figure 33. Discounting (varied between 0% and 6% for costs and outcomes simultaneously) and the utility increment after reaching SVR (varied between 0.002 and 0.17) have the greatest impact. Except for a value of 6% for the discount rates for costs and outcomes, all ICERs are below £20,000/QALY.

Figure 33 Tornado diagram for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT3 TE IFN eligible



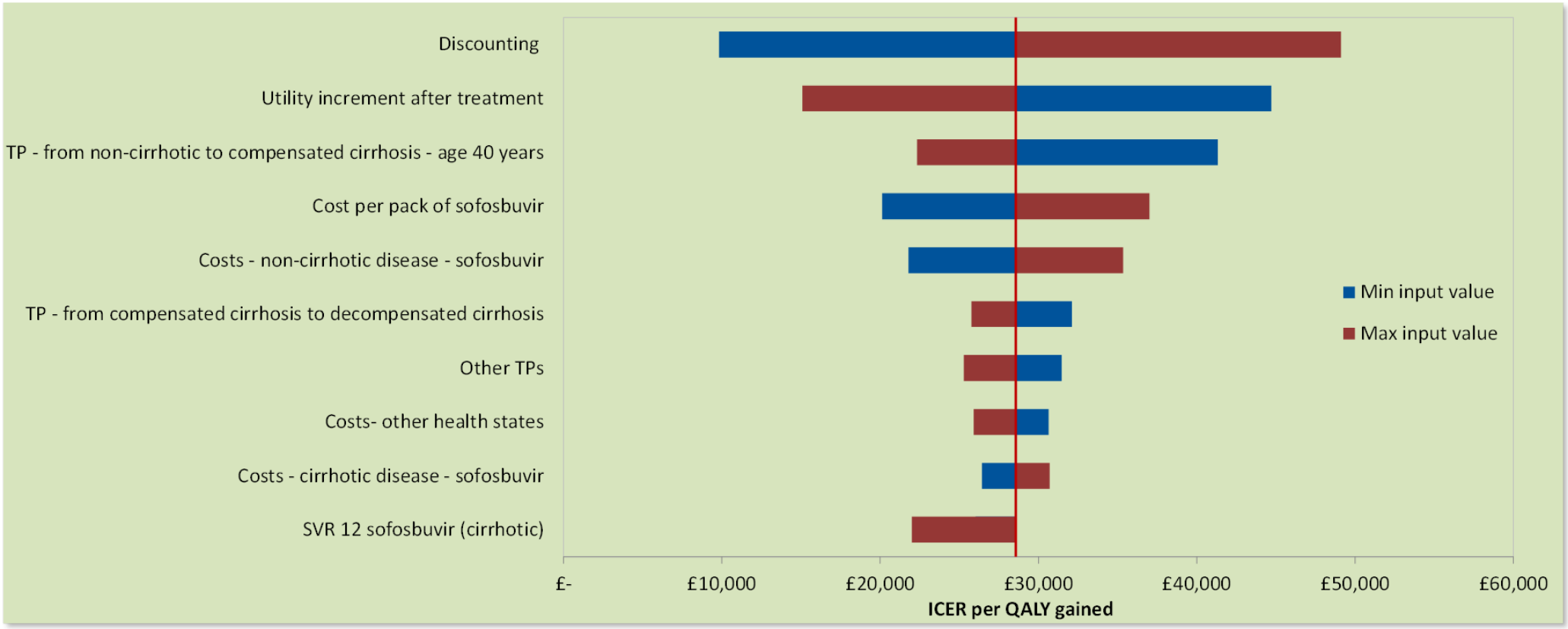
Note: The results for SOF + RBV for 24 weeks are presented in appendix (section **Error! Reference source not found.**).

Genotype 3 treatment-experienced unsuitable for interferon

SOF + RBV (24 weeks) versus No treatment

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir and RBV (24 weeks) compared with no treatment is shown to be £28,569/QALY (Table 81). The tornado chart is shown in Figure 34. Discounting (varied between 0% and 6% for costs and outcomes simultaneously) and the utility increment after reaching SVR (varied between 0.002 and 0.17) have the greatest impact, originating ICERs of greater than £40,000/QALY.

Figure 34 Tornado diagram for SOF+RBV (24 weeks) versus NT in GT3 TE unsuitable for IFN

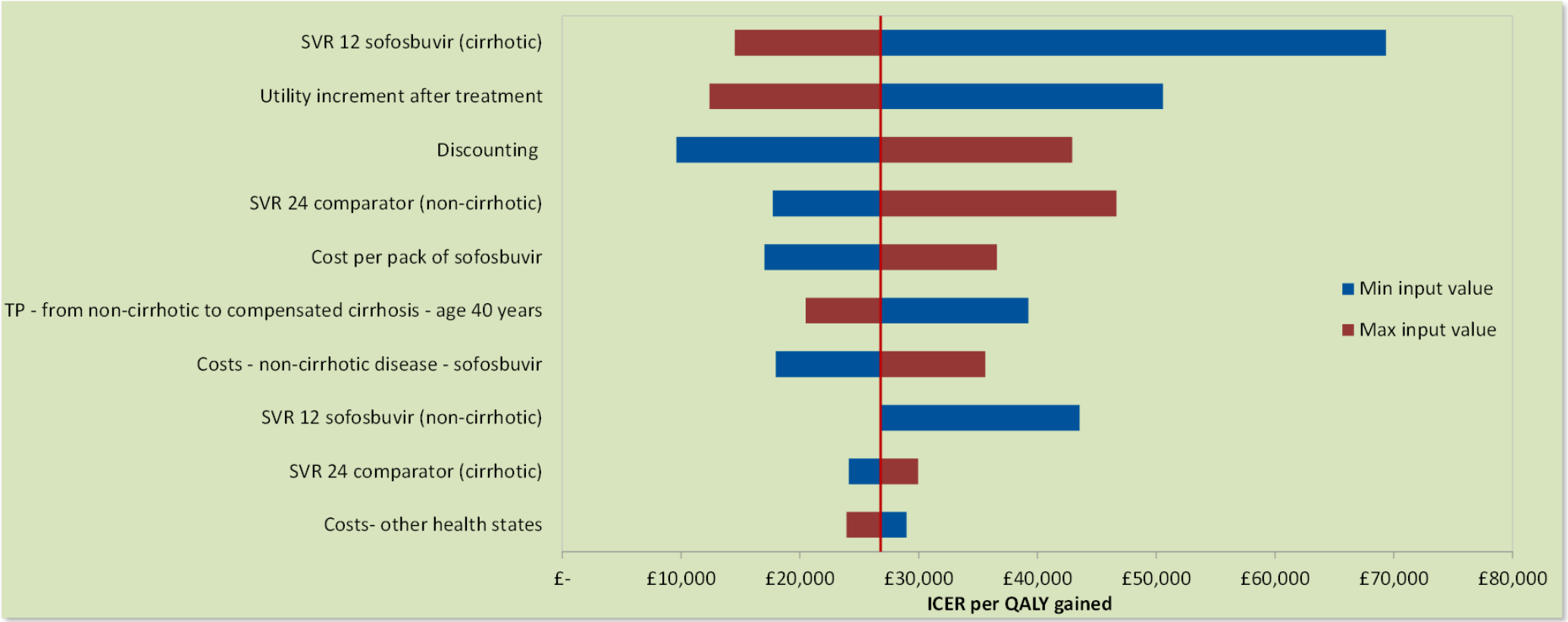


Genotype 4/5/6 treatment-naïve

SOF + PEG-IFN-2a + RBV (12 weeks) versus PEG-IFN-2a + RBV (48 weeks)

For a time horizon of 100 years, the base case ICER per QALY gained for sofosbuvir, PEG-IFN and RBV (12 weeks) compared with PEG-IFN and RBV (48 weeks) is shown to be £26,797/QALY (Table 81). The tornado chart is shown in Figure 35. The SVR rate for cirrhotic patients on sofosbuvir (varied between 1.3% and 98.7%), the utility increment after reaching SVR (varied between 0.002 and 0.17), discounting (varied between 0% and 6% for costs and outcomes simultaneously) and the SVR rate for non-cirrhotic patients on PEG-IFN + RBV (varied between 26.6% and 73.4%) have the greatest impact on the results. Overall ICERs vary between £9,000 and £70,000/QALY.

Figure 35 Tornado diagram for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT4/5/6 TN



The base case SVR for cirrhotic patients on sofosbuvir is 100%. Therefore the maximum value of this input is also 100% and the ICER is therefore the same as the base case

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The probabilistic sensitivity analysis (PSA) performed on each genotype and treatment history which included 1000 simulations is presented according to comparator as follows. ICERs calculated in the PSA are for sofosbuvir against each comparator treatment.

Genotype 1 treatment-naïve interferon eligible

SOF + PEG-IFN-2a + RBV (12 weeks) versus PEG-IFN + RBV (48 weeks)

The probability that SOF + PEG-IFN + RBV (12 weeks) is a cost-effective option over PEG-IFN + RBV (48 weeks) is approximately 90% at a £30,000 threshold and approximately 63% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 36 and Figure 37, respectively.

Figure 36 Cost-effectiveness plane for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT1 TN IFN eligible

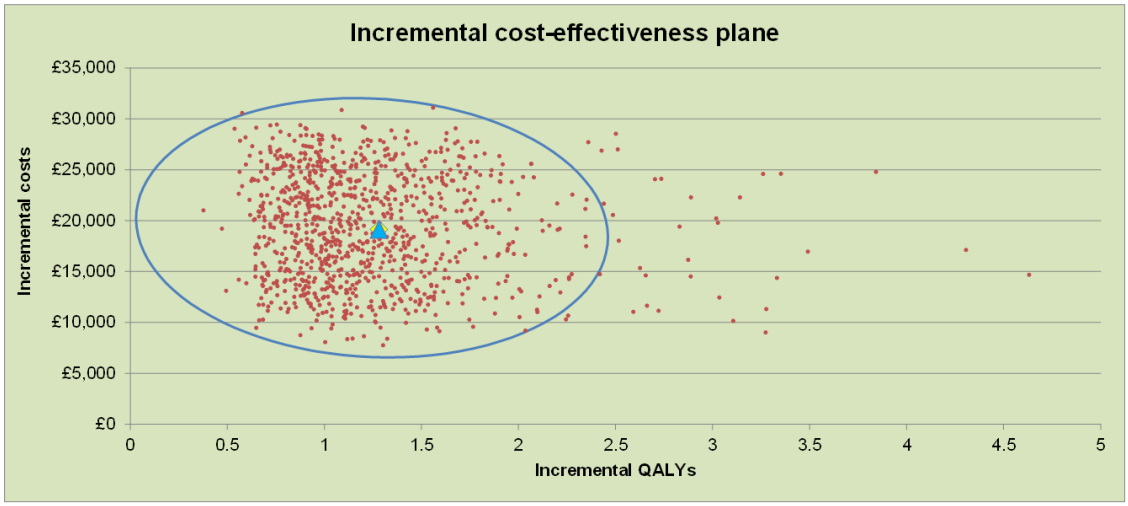
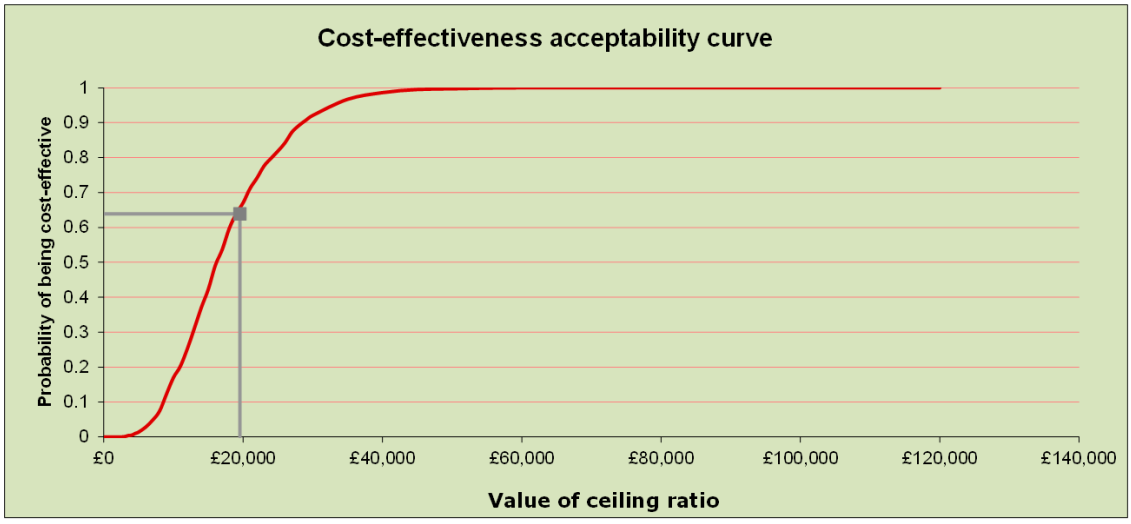


Figure 37 Cost-effectiveness acceptability curve for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT1 TN IFN eligible



SOF + PEG-IFN-2a + RBV (12 weeks) versus Telaprevir + PEG-IFN-2a + RBV

The probability that SOF + PEG-IFN + RBV (12 weeks) is a cost-effective option over telaprevir + PEG-IFN+ RBV is estimated to be approximately 85% at a £30,000 threshold and approximately 68% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 38 and Figure 39, respectively. The cost-effectiveness plane also shows

that the sofosbuvir regimen has a probability of 20% to become the dominant strategy, and therefore cost-saving, compared to the telaprevir regimen.

Figure 38 Cost-effectiveness plane for SOF+PEG-IFN-2a+RBV (12 weeks) versus TPV+PEG-IFN-2a+RBV in GT1 TN IFN eligible

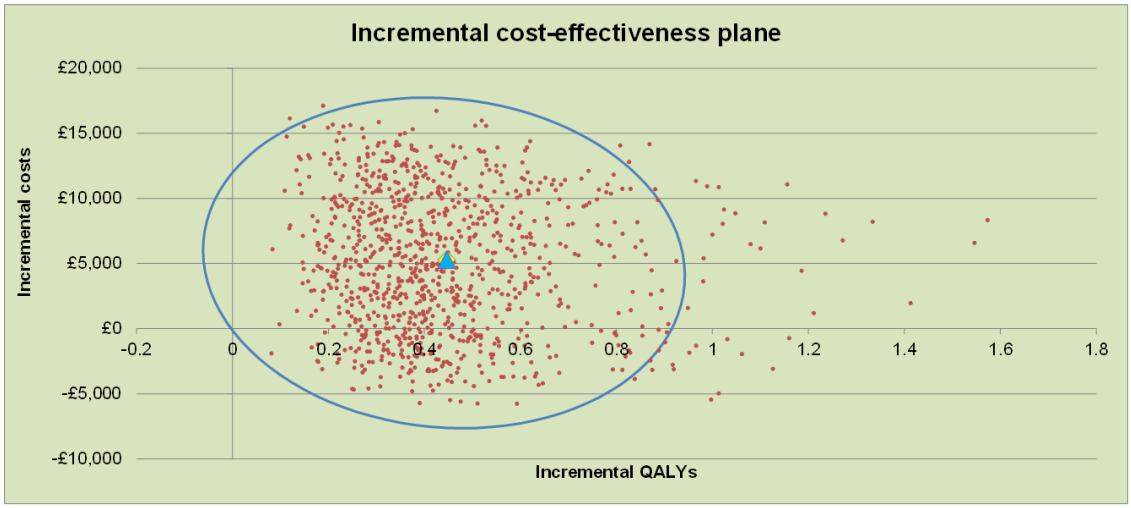
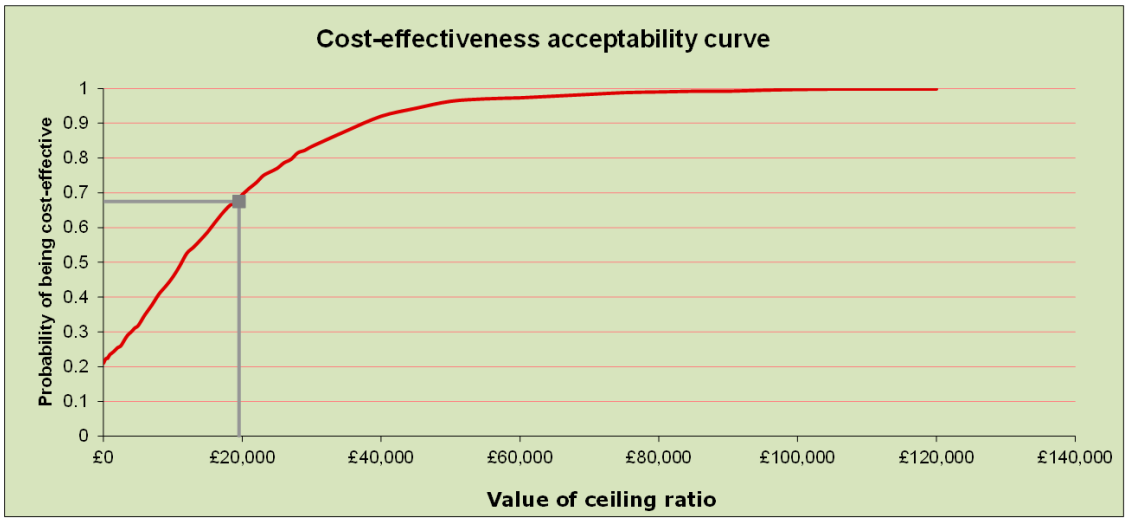


Figure 39 Cost-effectiveness acceptability curve for SOF+PEG-IFN-2a+RBV (12 weeks) versus TPV+PEG-IFN-2a+RBV in GT1 TN IFN eligible



SOF + PEG-IFN-2a + RBV (12 weeks) versus Boceprevir + PEG-IFN-2b + RBV

The probability that SOF + PEG-IFN + RBV (12 weeks) is a cost-effective option compared to boceprevir + PEG-IFN-2b + RBV at a £30,000 threshold is estimated to be approximately 95%. The cost effectiveness at a £20,000 threshold is estimated to be approximately 85%. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 40 and Figure 41, respectively. The cost-effectiveness plane also shows that the sofosbuvir regimen has a probability of 20% to become the dominant strategy, and therefore cost-saving, compared to the boceprevir regimen.

Figure 40 Cost-effectiveness plane for SOF+PEG-IFN-2a+RBV (12 weeks) versus BOC+PEG-IFN-2b+RBV (48 weeks) in GT1 TN IFN eligible

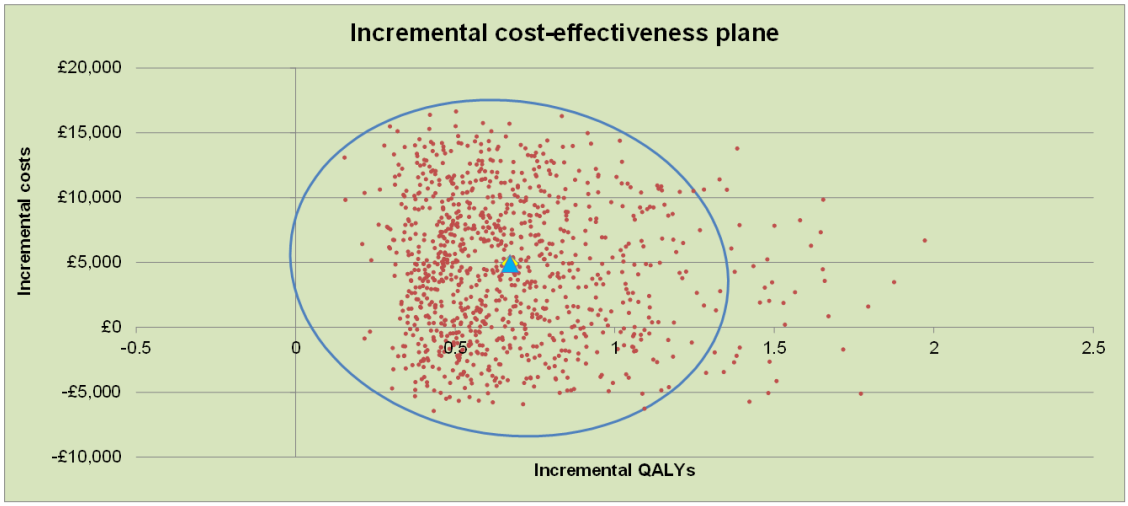
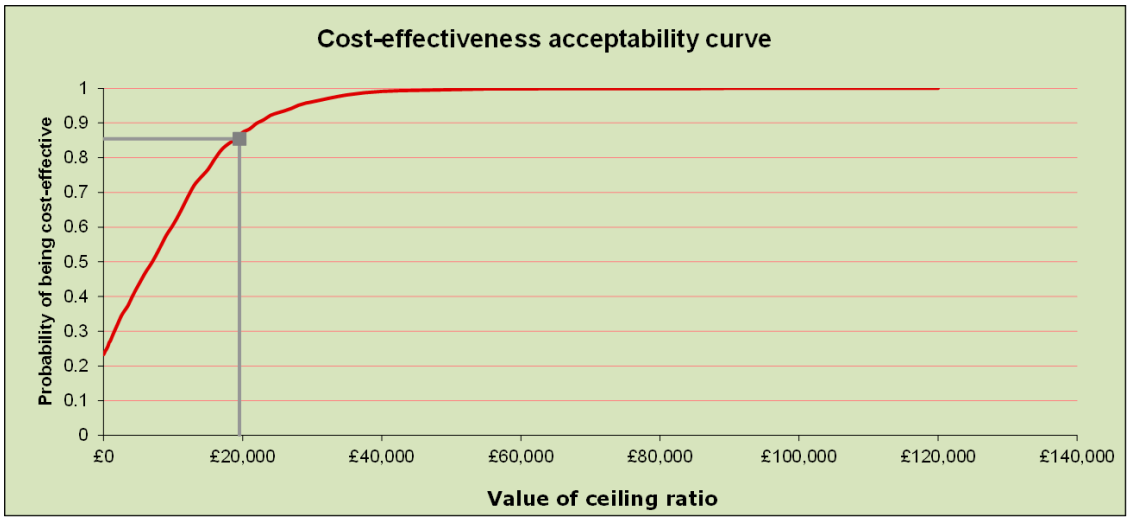


Figure 41 Cost-effectiveness acceptability curve for SOF+PEG-IFN-2a+RBV (12 weeks) versus BOC+PEG-IFN-2b+RBV (48 weeks) in GT1 TN IFN eligible



Genotype 1 treatment-naïve unsuitable for interferon

SOF + RBV (24 weeks) versus No treatment

The probability that SOF + RBV (24 weeks) is a cost-effective option over no treatment at a £30,000 threshold is estimated to be approximately 10% and less than 5% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 42 and Figure 43, respectively.

Figure 42 Cost-effectiveness plane for SOF+RBV (24 weeks) versus NT in GT1 TN unsuitable for IFN

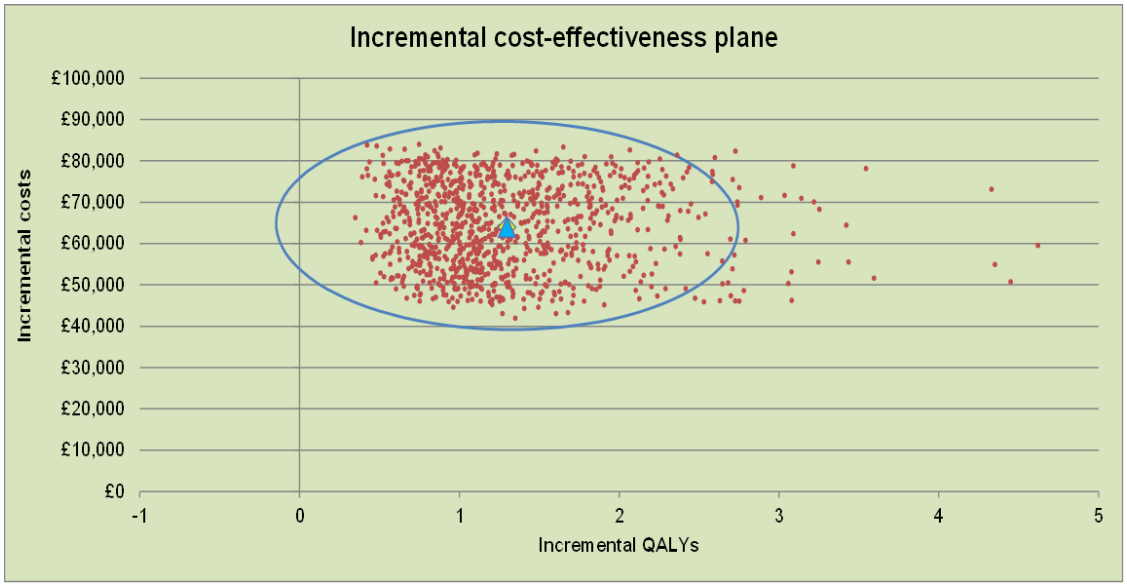
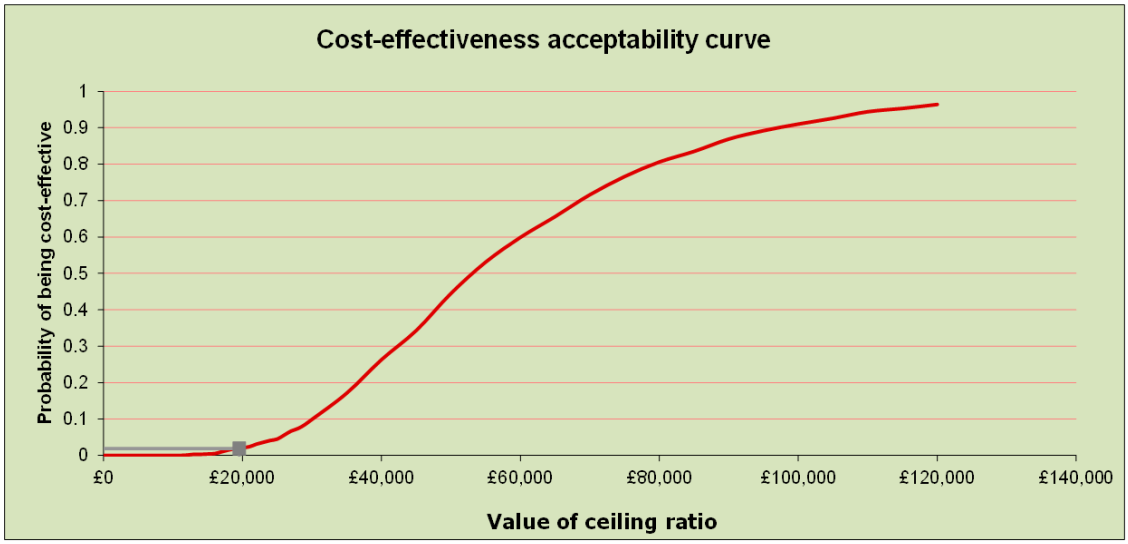


Figure 43 Cost-effectiveness acceptability for SOF+RBV (24 weeks) versus NT in GT1 TN unsuitable for IFN



Genotype 2 treatment-naïve interferon eligible

SOF + RBV (12 weeks) versus PEG-IFN-2a + RBV (24 weeks)

The probability that SOF + RBV (12 weeks) is a cost-effective option compared with PEG-IFN-2a + RBV at a £30,000 threshold is estimated to be approximately 10% and less than 5% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 44 and Figure 45, respectively.

Figure 44 Cost effectiveness plane for SOF+RBV (12 weeks) versus PEG-IFN-2a+RBV (24 weeks) in GT2 TN IFN eligible

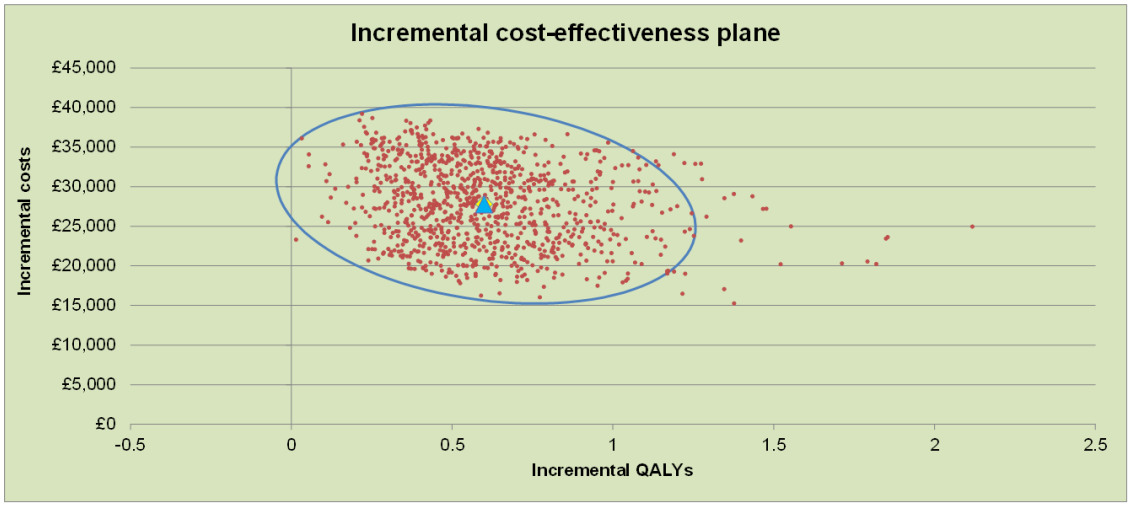
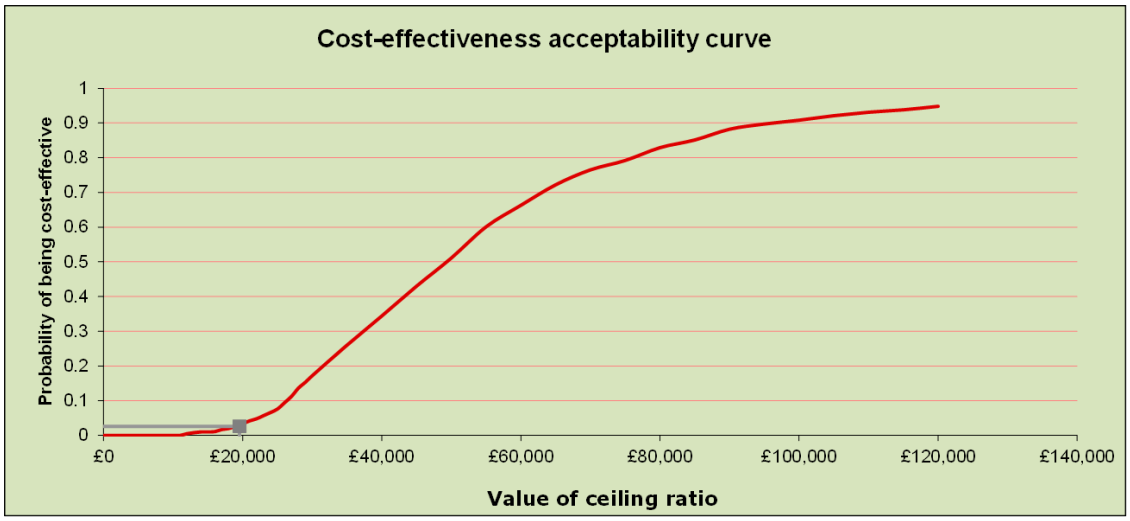


Figure 45 Cost-effectiveness acceptability for SOF+RBV (12 weeks) versus PEG-IFN-2a+RBV (24 weeks) in GT2 TN IFN eligible



Genotype 2 treatment-naïve unsuitable for interferon

SOF + RBV (12 weeks) versus No treatment

The probability that SOF + RBV (12 weeks) is a cost-effective option compared with no treatment at a £30,000 threshold is estimated to be near 100% and approximately 98% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 46 and Figure 47, respectively.

Figure 46 Cost-effectiveness plane for SOF+RBV (12 weeks) versus NT in GT2 TN unsuitable for IFN

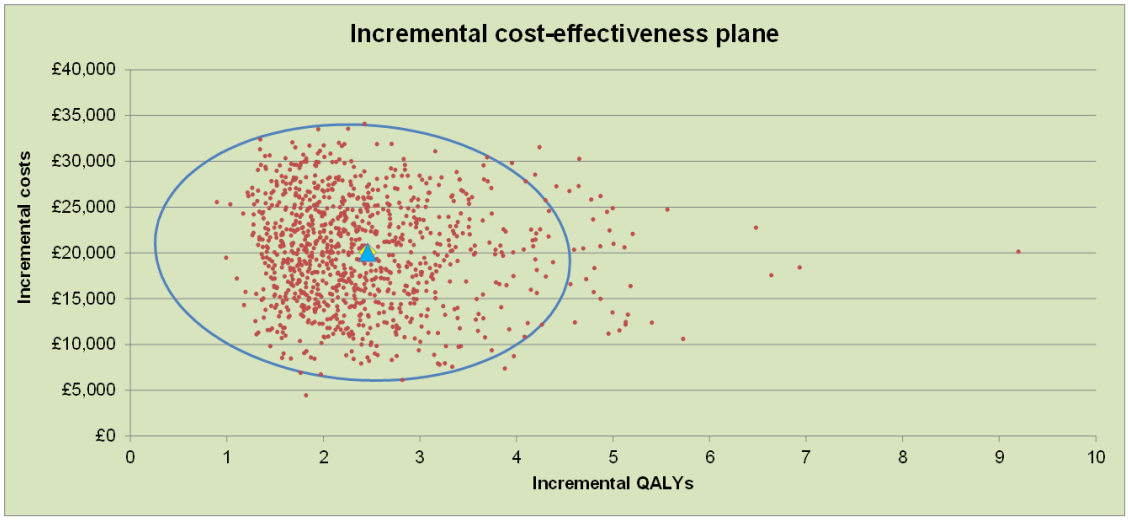
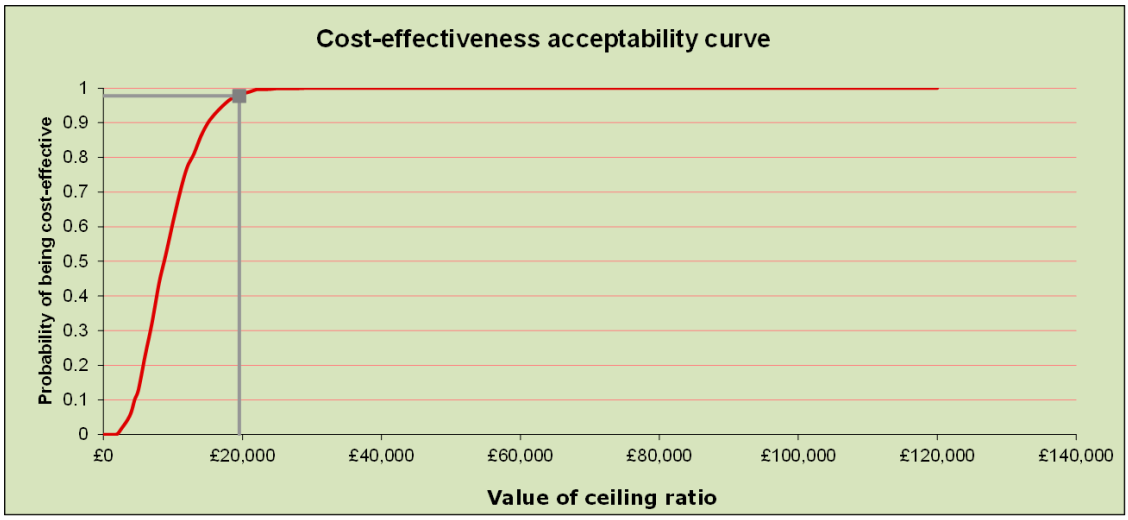


Figure 47 Cost-effectiveness acceptability for SOF+RBV (12 weeks) versus NT in GT2 TN unsuitable for IFN



Genotype 2 treatment-experienced interferon eligible

SOF + RBV (12 weeks) versus No treatment

The probability that SOF + RBV (12 weeks) is a cost-effective option compared with no treatment at a £30,000 threshold is estimated to be near 100% and approximately 95% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 48 and Figure 49, respectively.

Figure 48 Cost-effectiveness plane for SOF+RBV (12 weeks) versus NT in GT2 TE IFN eligible

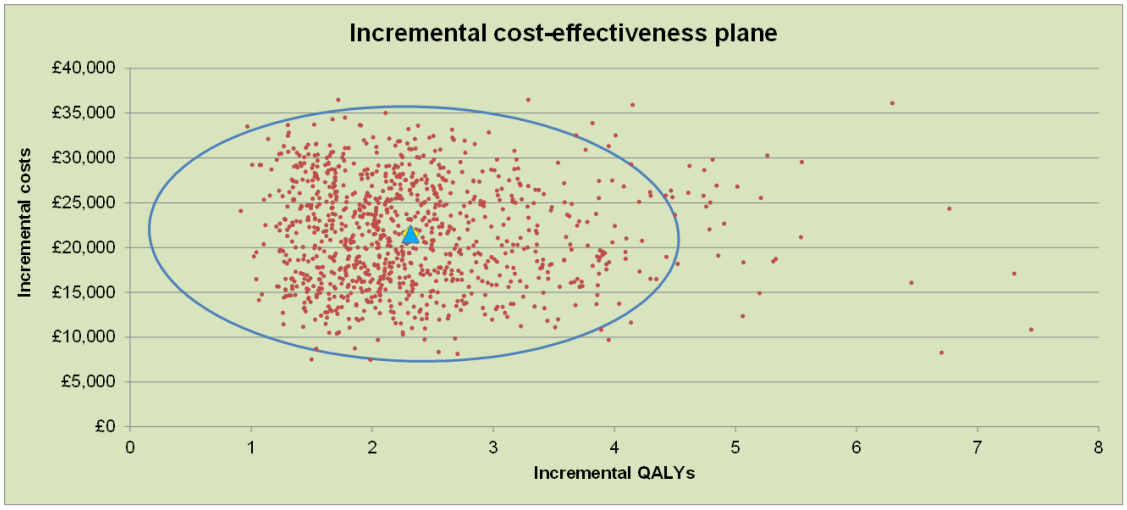
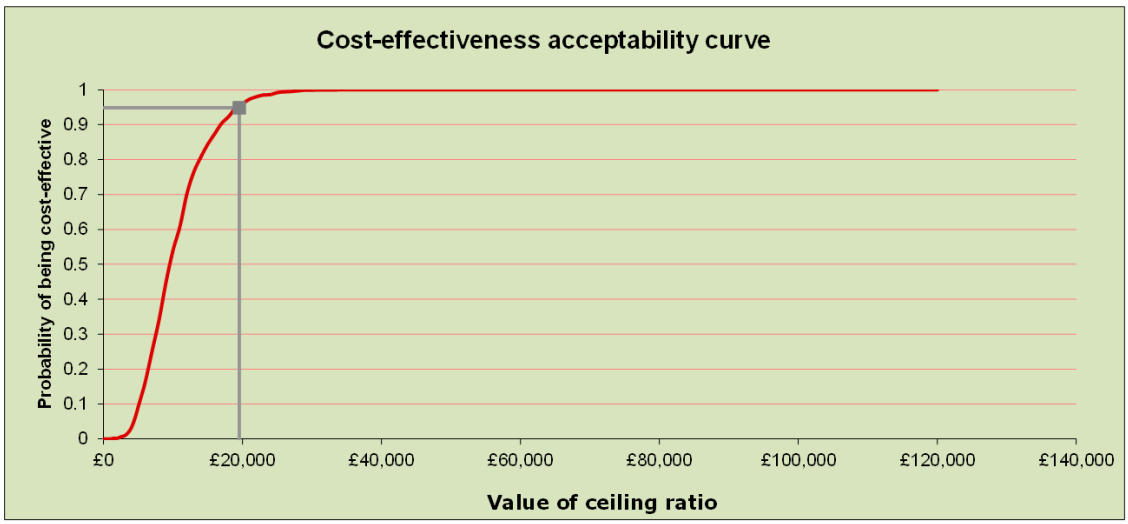


Figure 49 Cost-effectiveness acceptability for SOF+RBV (12 weeks) versus NT in GT2 TE IFN eligible



SOF + RBV (12 weeks) versus PEG-IFN-2a + RBV (48 weeks)

The probability that SOF + RBV (12 weeks) is a cost-effective option compared with PEG-IFN-2a + RBV at a £30,000 threshold is estimated to be approximately 95% and approximately 78% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 50 and Figure 51, respectively.

Figure 50 Cost-effectiveness plane for SOF+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT2 TE IFN eligible

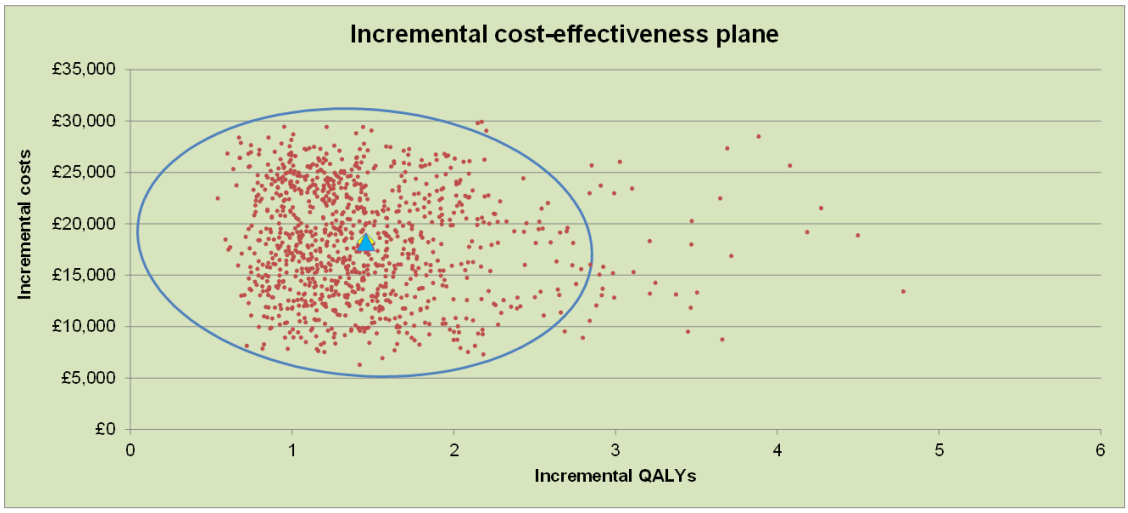
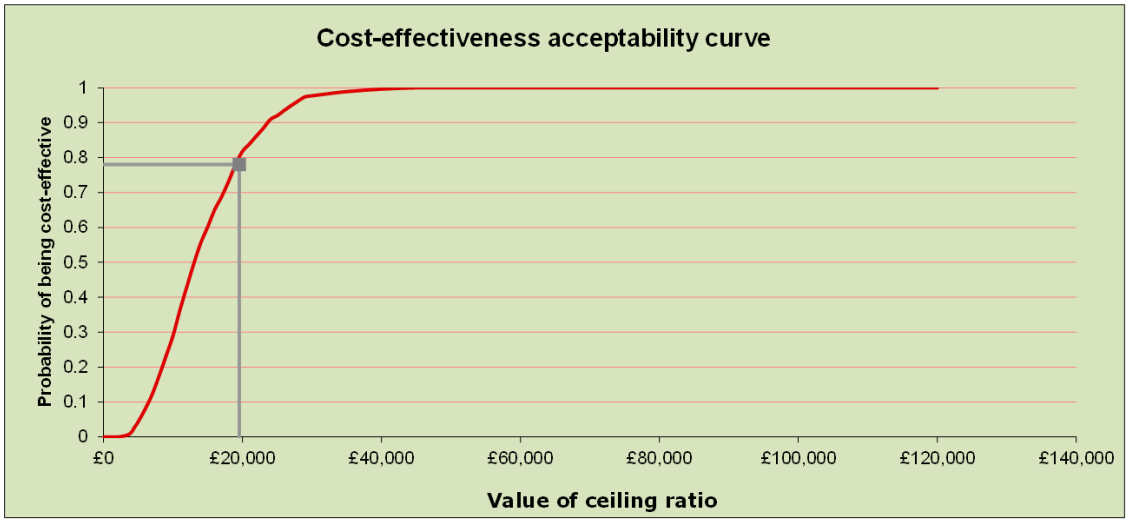


Figure 51 Cost-effectiveness acceptability for SOF+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT2 TE IFN eligible



Genotype 2 treatment-experienced unsuitable for interferon

SOF + RBV (12 weeks) versus No treatment

The probability that SOF + RBV (12 weeks) is a cost-effective option compared with no treatment at a £30,000 threshold is estimated to be near 100% and approximately 97% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 52 and Figure 53, respectively.

Figure 52 Cost-effectiveness plane for SOF+RBV (12 weeks) versus NT in GT2 TE unsuitable for IFN

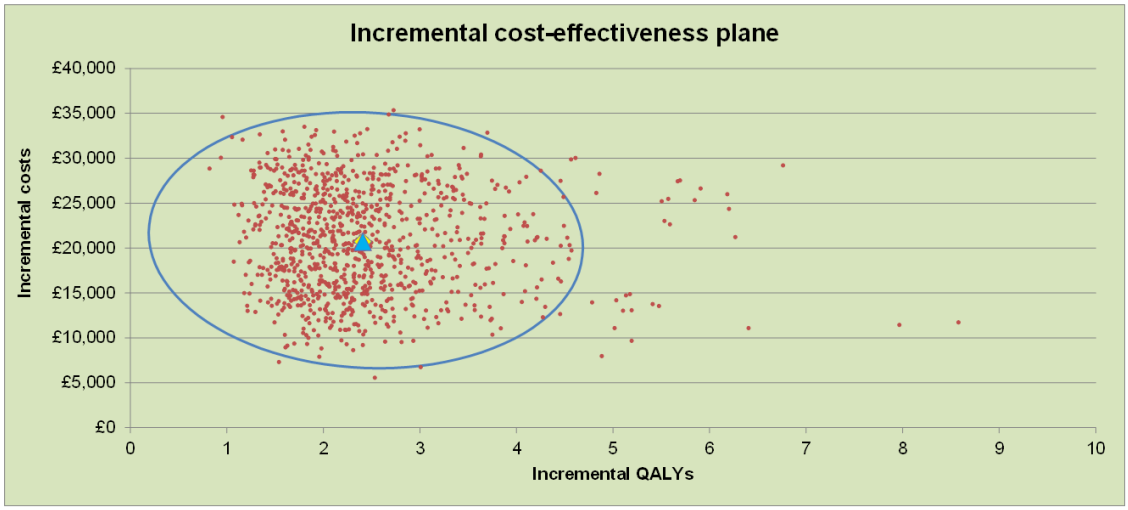
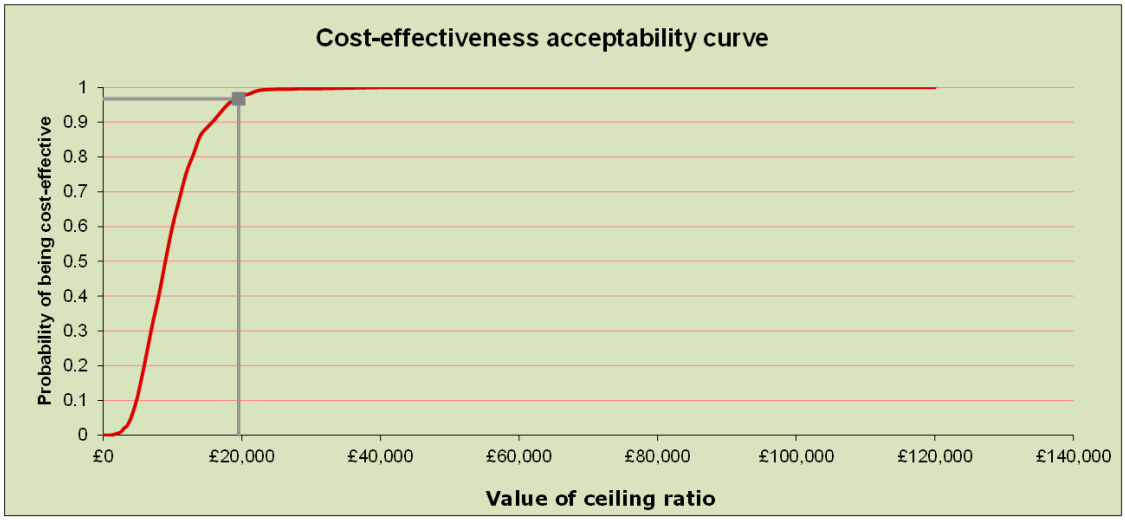


Figure 53 Cost-effectiveness acceptability for SOF+RBV (12 weeks) versus NT in GT2 TE unsuitable for IFN



Genotype 3 treatment-naïve interferon eligible

SOF + PEG-IFN-2a + RBV (12 weeks) versus PEG-IFN-2a + RBV (24 weeks)

The probability that SOF + PEG-IFN-2a + RBV (12 weeks) is a cost-effective option compared with PEG-IFN-2a + RBV at a £30,000 threshold is estimated to be approximately 80% and approximately 37% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 54 and Figure 55, respectively.

Figure 54 Cost-effectiveness plane for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (24 weeks) in GT3 TN IFN eligible

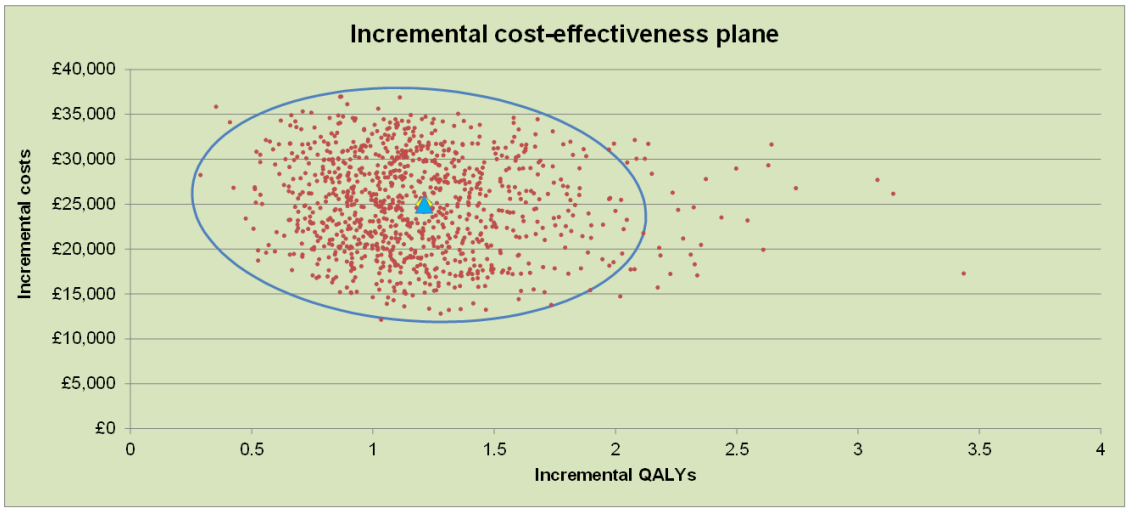
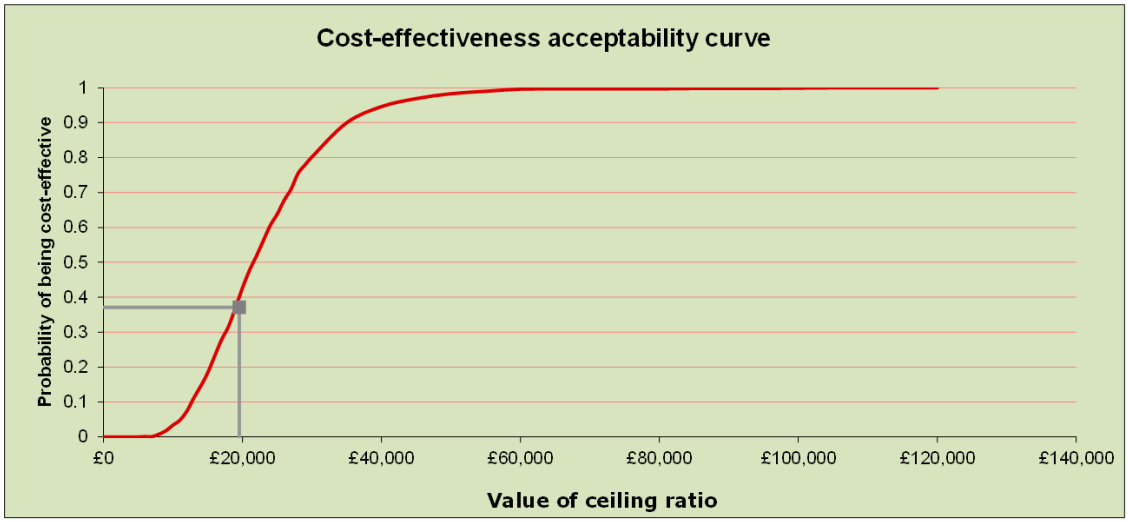


Figure 55 Cost-effectiveness acceptability curve for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (24 weeks) in GT3 TN IFN eligible



The results for SOF + RBV for 24 weeks are presented in appendix (section **Error! Reference source not found.**).

Genotype 3 treatment-naïve unsuitable for interferon

SOF + RBV (24 weeks) versus No treatment

The probability that SOF + RBV (24 weeks) is a cost-effective option compared with no treatment at a £30,000 threshold is estimated to be approximately 80% and approximately 30% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 56 and Figure 57, respectively.

Figure 56 Cost-effectiveness plane for SOF+RBV (24 weeks) versus NT in GT3 TN unsuitable for IFN

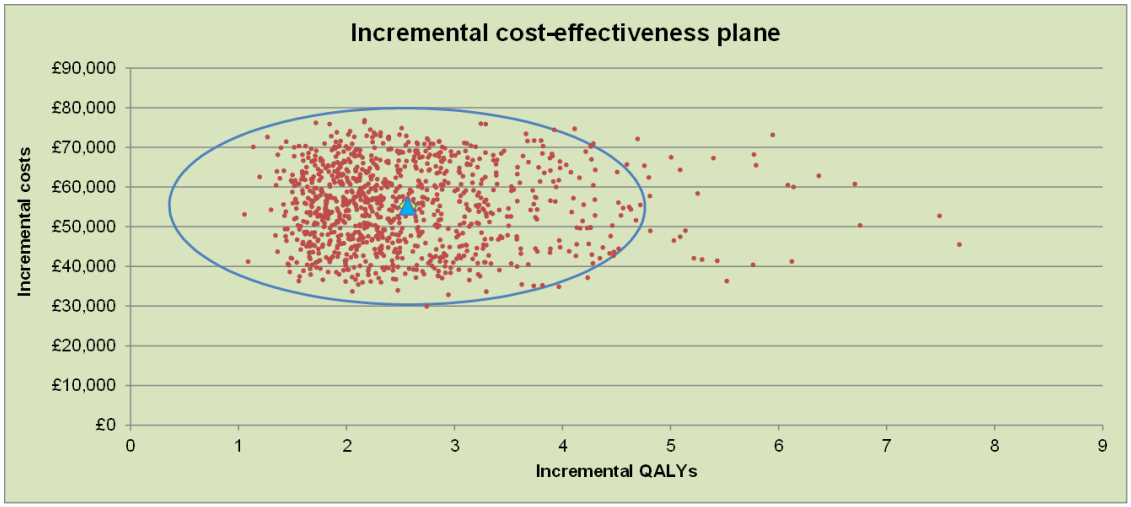
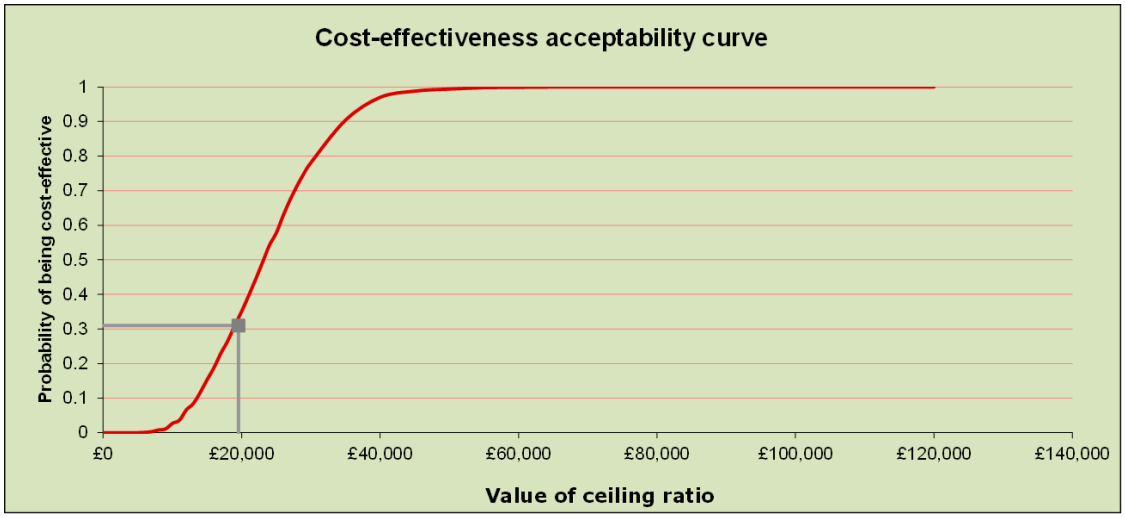


Figure 57 Cost-effectiveness acceptability curve for SOF+RBV (24 weeks) versus NT in GT3 TN unsuitable for IFN



Genotype 3 treatment-experienced interferon eligible

SOF + PEG-IFN-2a + RBV (12 weeks) versus No treatment

The probability that SOF + PEG-IFN-2a + RBV (12 weeks) is a cost-effective option compared with no treatment at a £30,000 threshold is estimated to be near 100% and approximately 96% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 58 and Figure 59, respectively.

Figure 58 Cost-effectiveness plane for SOF+PEG-IFN-2a+RBV (12 weeks) versus NT in GT3 TE IFN eligible

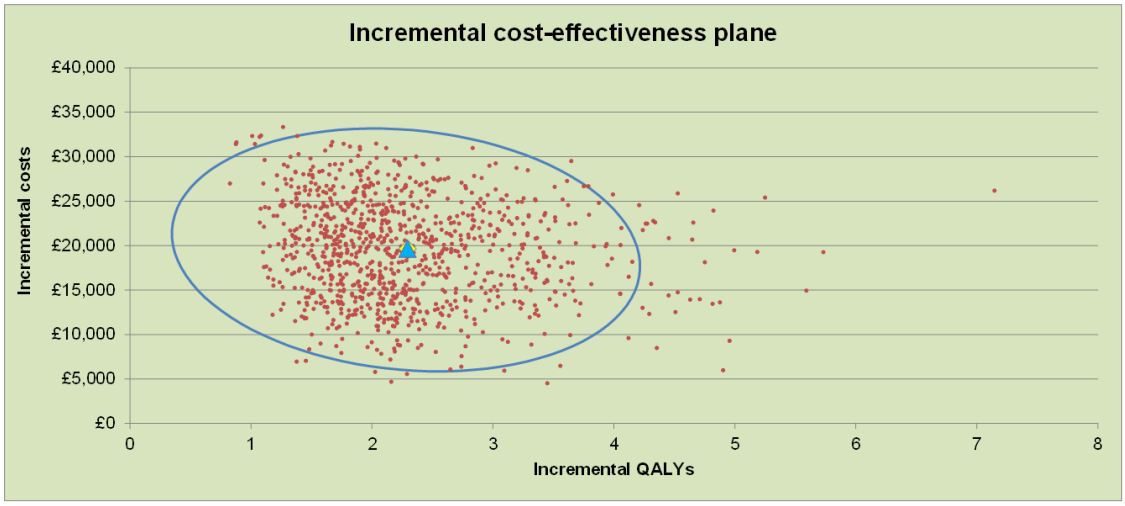
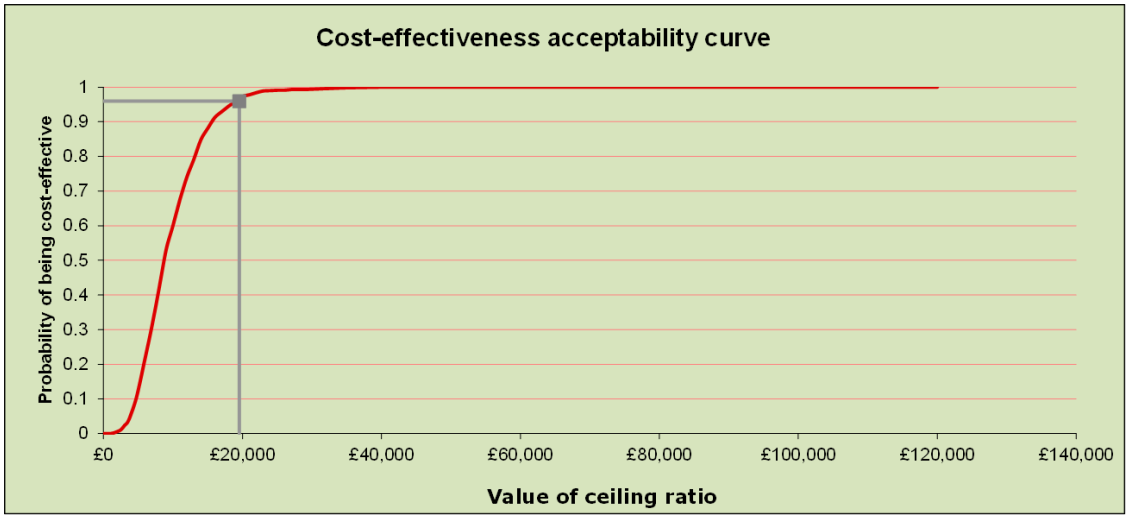


Figure 59 Cost-effectiveness acceptability for SOF+PEG-IFN-2a+RBV (12 weeks) versus NT in GT3 TE IFN eligible



The results for SOF + RBV for 24 weeks are presented in appendix (section **Error! Reference source not found.**).

<u>SOF + PEG-IFN-2a + RBV (12 weeks) versus PEG-IFN-2a + RBV (48 weeks)</u>

The probability that SOF + PEG-IFN-2a + RBV (12 weeks) is a cost-effective option compared with PEG-IFN-2a + RBV at a £30,000 threshold is estimated to be approximately 98% and approximately 75% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 60 and Figure 61, respectively.

Figure 60 Cost-effectiveness plane for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT3 TE IFN eligible

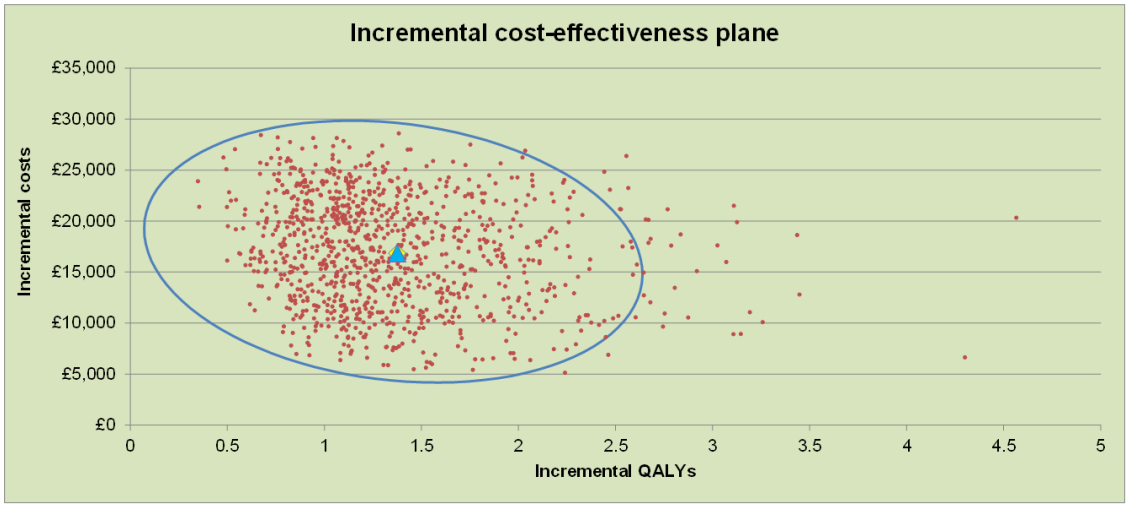
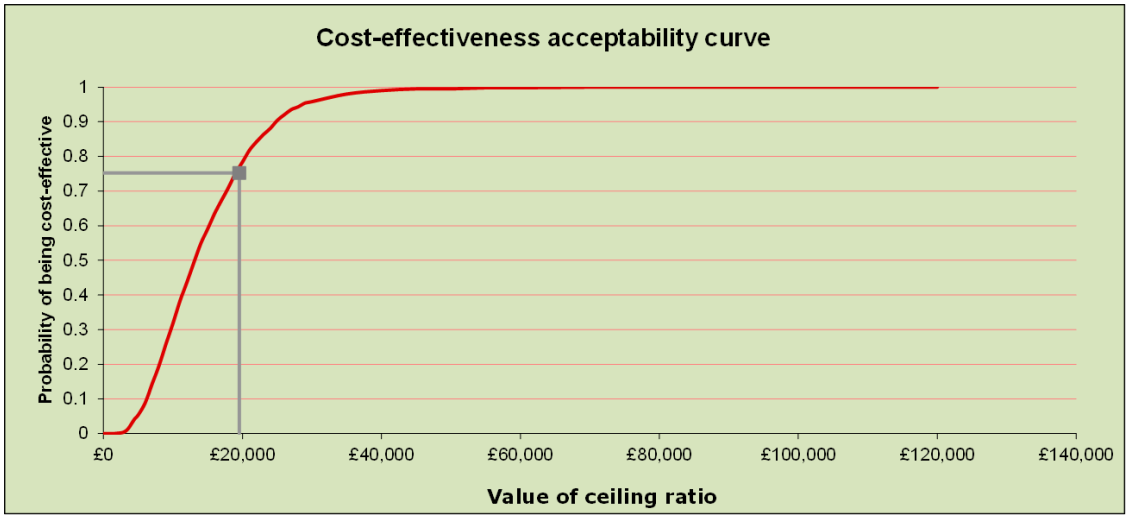


Figure 61 Cost-effectiveness acceptability for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT3 TE IFN eligible



The results for SOF + RBV for 24 weeks are presented in appendix (section **Error! Reference source not found.**).

Genotype 3 treatment-experienced unsuitable for interferon

SOF + RBV (24 weeks) versus No treatment

The probability that SOF + RBV (24 weeks) is a cost-effective option compared with no treatment at a £30,000 threshold is estimated to be approximately 48% and approximately 12% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 62 and Figure 63, respectively.

Figure 62 Cost-effectiveness plane for SOF+RBV (24 weeks) versus NT in GT3 TE unsuitable for IFN

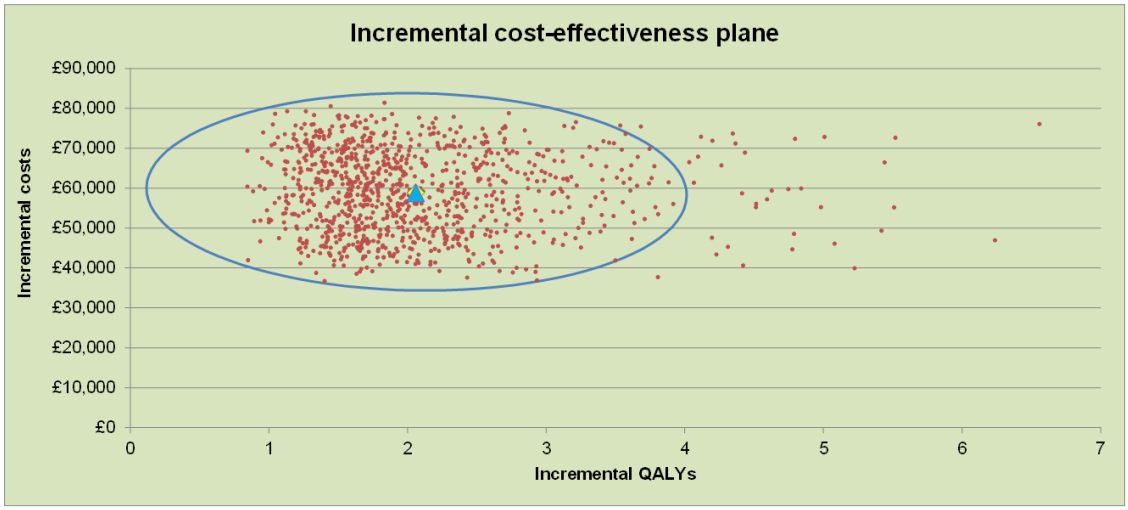
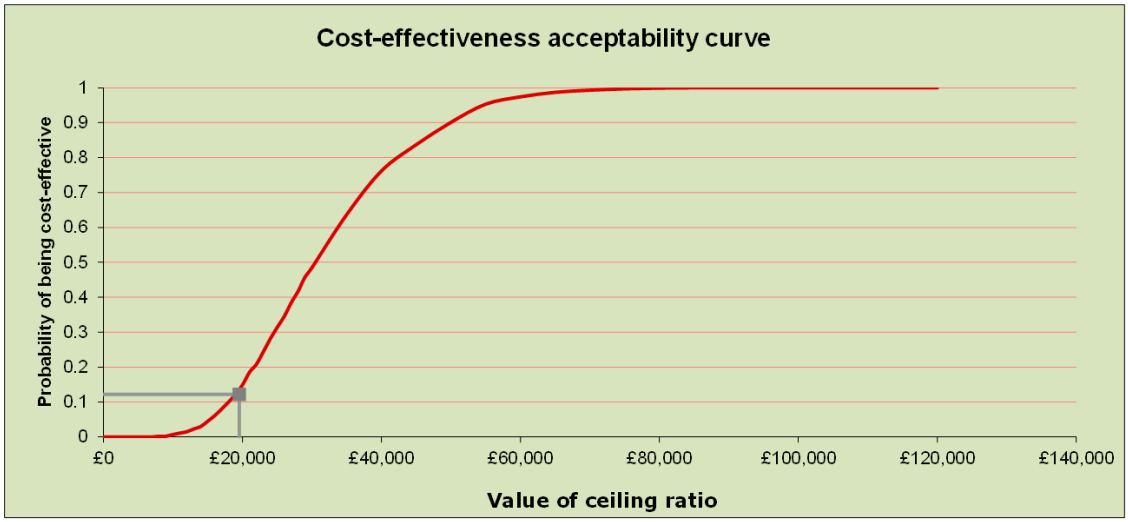


Figure 63 Cost-effectiveness acceptability curve for SOF+RBV (24 weeks) versus NT in GT3 TE unsuitable for IFN



Genotype 4/5/6 treatment-naïve

SOF + PEG-IFN-2a + RBV (12 weeks) versus PEG-IFN-2a + RBV (48 weeks)

The probability that SOF + PEG-IFN-2a + RBV (12 weeks) is a cost-effective option compared with PEG-IFN-2a + RBV at a £30,000 threshold is estimated to be approximately 50% and approximately 24% at a £20,000 threshold. The cost-effectiveness plane and the cost-effectiveness acceptability curve are shown in Figure 64 and Figure 65, respectively.

Figure 64 Cost-effectiveness plane for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT4/5/6 TN

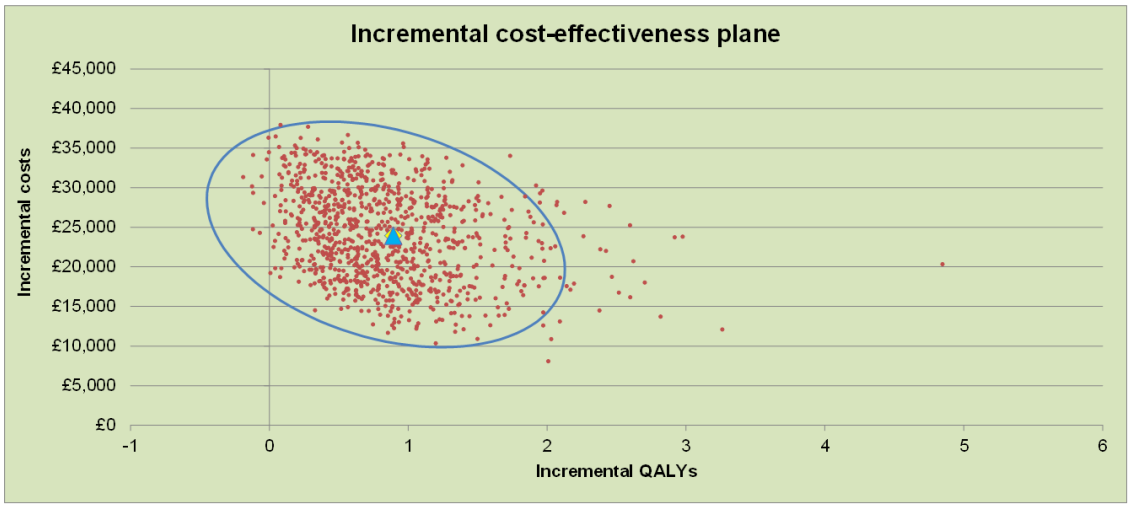
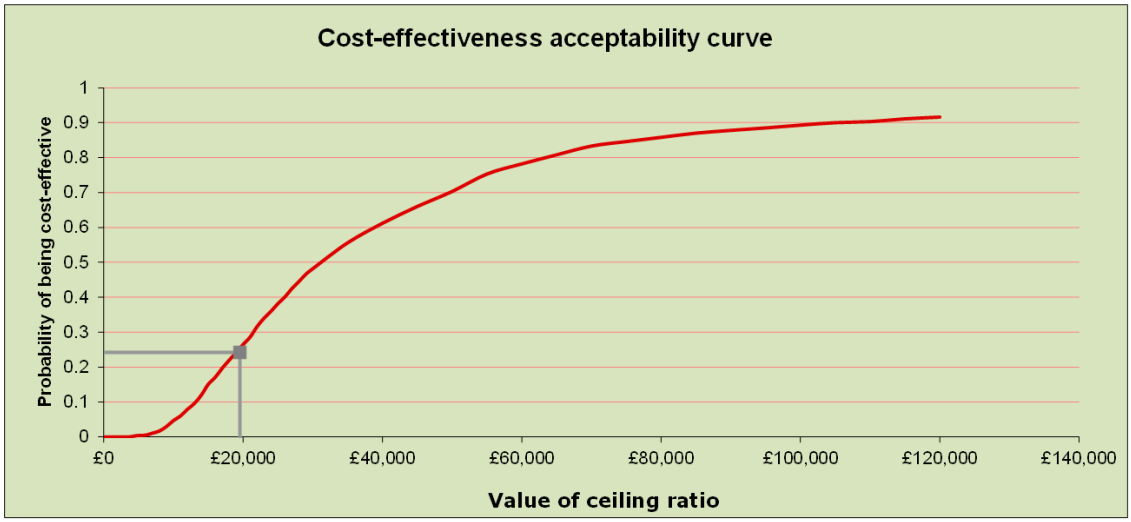


Figure 65 Cost-effectiveness acceptability for SOF+PEG-IFN-2a+RBV (12 weeks) versus PEG-IFN-2a+RBV (48 weeks) in GT4/5/6 TN



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The deterministic sensitivity analysis assessed the impact of incorporating re-infection and recurrence in the model and concluded that the economic results are not sensitive to this structural change.

7.7.10 What were the main findings of each of the sensitivity analyses?

The deterministic sensitivity analysis shows that overall the economic results are sensitive to the discount rates for both costs and outcomes and the utility increment after reaching SVR. For some patient populations the results were also sensitive to changes in the SVR rate for cirrhotic patients on the comparator treatment. Nevertheless, sofosbuvir continues to be cost-effective in all scenarios (for a £20,000/QALY threshold) in the following patient populations:

- Genotype 2 treatment-naïve and treatment-experienced unsuitable for interferon
- Genotype 2 and 3 treatment-experienced interferon eligible against no treatment

Variation of the main drivers of the results originated ICERs slightly over £20,000/QALY in the following patient populations:

- Genotype 1 treatment-naïve interferon eligible against PEG-IFN and boceprevir
- Genotype 2 treatment-experienced interferon eligible against PEG-IFN
- Genotype 3 treatment-experienced interferon eligible against PEG-IFN

Variation of the main drivers of the results originated ICERs slightly over £30,000/QALY in the following patient populations:

- Genotype 1 treatment-naïve interferon eligible against telaprevir
- Genotype 3 treatment-naïve unsuitable for interferon
- Genotype 3 treatment-naïve interferon eligible against PEG-IFN

The results of the sensitivity analysis show that ICERs for the sofosbuvir regimen in genotype 1, treatment-naïve, unsuitable for interferon, genotype 2, treatment-naïve, interferon eligible (against PEG-IFN + RBV) and genotype 3, treatment-experienced, unsuitable for interferon could be cost-effective if a discount rate of 6% (for both costs and outcomes) was used. Furthermore, in genotype 3, treatment-experienced, unsuitable for interferon variation of the utility increment after reaching SVR could also lead to cost-effective results.

ICERs for genotype 3 treatment-naïve are just over £20,000/QALY (Table 81). The sensitivity analysis shows that the results could be cost-effective if we vary input parameters such as the discount rates, the utility increment after reaching SVR, the SVR rates for cirrhotic patients, the transition probabilities to more advanced states of the disease and as the costs of these states.

Finally, the sensitivity analysis for GT4/5/6 treatment-naïve shows that the sofosbuvir regimen would be cost-effective at a £20,000/QALY threshold by varying the SVR rate for cirrhotic patients on sofosbuvir, the discount rates and the utility increment after reaching SVR.

7.7.11 What are the key drivers of the cost-effectiveness results?

See section 7.7.7

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.

The model underwent internal and external validation.

In the internal validation two distinct quality assessments were made to the model. The first was conducted by a senior modeller and a senior statistician with previous experience in HCV. The second check was made by a second modeller not familiar with the project.

The model was externally validated with one clinical expert from England. As mentioned previously this clinical expert was selected based upon the role within the NHS as a senior Consultant at a regional CHC treatment center that treats more than 100 CHC patients per year. An initial meeting was set to discuss:

- Model structure and underlying assumptions
- Best clinical data to use for the comparator treatments based on available literature
- Resource use during treatment and treatment pattern
- Adequacy of health state costs obtained from the literature

A final meeting occurred after the model was developed to review the model inputs and results and incorporate any comments/suggestions.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

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.

Not applicable

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable

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).

Not applicable

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.

Not applicable

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 any sofosbuvir regimen in GT1, 2, 3, 4, 5 or 6.

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 results of this economic evaluation are relevant to all groups of patients defined in section 5 as the clinical data included in the model reflects that from the Phase III clinical trials on these patients. However, the licence for sofosbuvir also covers treatment-experienced patients with HCV GT 1 infection. The SVR for this patient group was extrapolated based on an FDA model and as such no economic analysis was conducted for this subgroup. Furthermore, sofosbuvir is also licensed for pre-transplant patients.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths of the evaluation

The modelling approach was deemed the most adequate to reflect the natural history of HCV. By choosing a Markov model the costs, QALYs and clinical effectiveness can be extrapolated beyond the duration of the trials to assess the long-term impact of this new regimen.

The model structure is similar to that used in previous developed cost-effectiveness analyses and NICE HCV HTAs[135;139]. The difference is that to reflect the data available from the sofosbuvir trials, the mild and moderate health states were combined into a single non-cirrhotic health state to reflect patient's disease severity at baseline.

The analysis incorporated all important health effects, that is, SVRs, AEs and HRQoL. The model was populated with clinical data from the Phase II and III clinical trials on sofosbuvir supporting the licensed indication, providing a direct comparison between the currently available treatments in the NHS for each patient group and the licensed dose of sofosbuvir. The data for the clinical effectiveness of the comparator treatments was obtained from the Phase III clinical trials, when available, and from a systematic literature review. A systematic literature review was also conducted to obtain information on utilities, transition probabilities, health state costs and resource use while monitoring during treatment. The inputs selected for the model were considered the most appropriate by NICE in previous cost-effectiveness analyses.

The distribution of patients according to cirrhosis state is based on a broad UK registry increasing the reliability and applicability of the results to the HCV population awaiting treatment. Similarly, management of adverse events is also reflective of UK practice as validated by external experts.

Extensive deterministic and probabilistic sensitivity analysis was conducted by varying several input parameters. In general, the results were robust to variations in these parameters and the ICERs for the cost-effective patient groups did not significantly exceed £20,000/QALY or £30,000/QALY.

The model was thoroughly validated by two internal modellers and a statistician and externally validated by a clinical expert in the area of HCV.

Weaknesses of the evaluation

The biggest limitation of this analysis is due to the lack of published data for non-cirrhotic (F0-F3) and cirrhotic (F4) patients for all the comparator treatments. While in some cases data was completely absent, in other cases it was unreliable (i.e. a MTC was not feasible). Therefore some assumptions had to be made. For example, Roberts et al. 2009[165] is the only publication providing SVR rates split by non-cirrhotic and cirrhotic for PEG-IFN+RBV in genotype 1 treatment-naïve interferon eligible patients. However, only 6% of F4 patients reached SVR. Since this value was not considered reflective of clinical practice (it appeared too low), the SVR rates from McHutchison et al., 2009[159] were used to reflect a more conservative approach. However, these SVR rates were

reported for F0-F2 and for F3-F4 patients respectively meaning that they do not accurately reflect the split F0-F3 and F4 that was considered in the model for non-cirrhotic and cirrhotic patients.

As another example, due to a lack of data for SVRs after retreatment, a few assumptions have been made to determine the SVR for PEG-IFN-2a in GT2 and GT3 treatment-experienced IFN eligible patients (both cirrhotic and non-cirrhotic). This parameter was calculated to be 35%, based on Lagging et al., 2013[171] using the distribution between relapsers and non-responders from Shoeb et al.,2011[172]. Discussions with clinical experts have suggested a slightly lower SVR rate in clinical practice and that they would follow current EASL guidance which states it would be very uncommon to retreat non GT1 patients who fail to achieve an SVR with PEG-IFN + RBV in the first instance (see appendix **Error! Reference source not found.**).

The cost of drugs is calculated assuming no wastage. This is particularly relevant for the ribavirin as for some treatment regimens the dose is based on weight. As noticed by NICE in the telaprevir STA[146] while patients are usually prescribed sufficient medication to last until the next visit, they can stop the medication half way through. In addition to this, the calculation of treatment costs is based on the average treatment duration which may not accurately reflect the cost of drugs prescribed. Nevertheless, the results of the sensitivity analyses around the cost of non-cirrhotic and cirrhotic disease while on treatment were included in the analysis.

The economic analyses do not consider the reduced HCV transmission due to improved treatment success associated with sofosbuvir relative to current treatment options. The potential benefit of sofosbuvir in alleviating the public health burden of HCV in England and Wales is therefore underestimated.

Finally, there is limited literature reporting SVR rates for GT2 and GT3 separately and therefore it is very difficult to find accurate SVR rates for some of the populations.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Sensitivity analyses around the age and weight at treatment start could have been included.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

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.

The Office of National Statistics (ONS) estimated that the population in England Wales and Northern Ireland was 56,996,200 in 2013. HCV has a prevalence of 0.41%; approximately 74% of which is chronic HCV[194]. Based on data from the ONS and HPA it is estimated that, in 2011, there were:

- 172,083 individuals chronically infected with hepatitis C in England and Wales
- 70,468 of which are diagnosed (the current diagnosis rate is estimated to be 41%[n]
- 20,000 of which are thought to be under treater care
- 9.000 (45%) are genotype 1; 1,460 (7.3%) are genotype 2; 8,760 (43.8%) are genotype 3; 780 (3.9%) are genotype 4/5/6 (Brant et al, 2010[195])
- 14,764 (74%) are treatment naïve and 5,236 treatment experienced
- 2,159 (14%) are IFN unsuitable and 17,841 IFN eligible
- 2,783 (14%) are cirrhotic and 17,217 non-cirrhotic

Among the treater care population, only 5,765 are eligible for receiving treatment in the first year. The barriers to treatment include advanced age, advanced liver damage, comorbidities, compliance, substance abuse but also capacity issues.

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[n] This comes from the following reference: Costella provides counts of laboratory reported cases annually and Goldberg provides similar data for Scotland (Costella and Goldberg, HPA report 2008). Estimated that 24% of patients were diagnosed at baseline in 2004 and approximately 2.75% diagnosed annually in years following 2004 based on estimated counts of treated patients derived through sales of pegylated inteferon, treatment rates, estimated rates of compliance / persistence. This diagnosed % was then updated with data in the 2012 HPA report.

Table 93 Number of patients (cirrhotic and non-cirrhotic) eligible for treatment over five years

Number of patients eligible for receiving treatment	2014	2015	2016	2017	2018
GT1					
TN, IFN eligible	1,334	1,474	1,776	1,995	2,155
TN, IFN unsuitable	60	52	18	15	15
TN, co-infected	447	542	612	664	699
Total GT1	1,841	2,069	2,406	2,674	2,869
GT2					
TN, IFN eligible	403	344	394	430	456
TN, IFN unsuitable	68	25	25	25	26
TE, IFN eligible	43	65	53	44	40
TE, IFN unsuitable	7	13	5	3	2
TN, co-infected	25	18	21	23	24
TE, co-infected	3	5	4	3	3
Total GT2	549	471	502	529	552
GT3					
TN, IFN eligible	1,735	1,544	1,781	1,950	2,072
TN, IFN unsuitable	291	109	109	109	110
TE, IFN eligible	228	369	346	325	333
TE, IFN unsuitable	37	71	32	22	18
TN, co-infected	795	604	714	780	821
TE, co-infected	103	180	160	143	147
Total GT3	3,189	2,878	3,142	3,328	3,500
GT4/5/6					
TN	185	184	209	226	237

GT, Genotype; TN, Treatment-naïve; TE, Treatment-experienced; IFN, Interferon

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

The current treatment options include pegylated-interferon alfa-2a or 2b with ribavirin (PR) for patients with all genotypes and protease inhibitors (PI) for genotype 1 patients (telaprevir and boceprevir in triple-therapy with PR). Estimates regarding the uptake of current technologies are based on current treatment patterns and Gilead market research.

The estimates detailed in Table 94 to Table 97 are based on an assumption that in the world without sofosbuvir, the market share for each current treatment of genotype 2, 3, 4/56 remains stable over the five-year time period (2014-2018) and the market share of PIs in genotype 1 increase gradually . The model assumes that no other treatment options will become available during that time. As such, in a world without sofosbuvir, patients who are unsuitable for IFN have no treatment options.

Table 94 Estimated market share for five years – world without SOF – GT1

	2014	2015	2016	2017	2018
GT1: TN mono-infected IFN eligible (cirrhotic and non-cirrhotic)					

Telaprevir+PEG-IFN-2a+RBV	30%	35%	40%	43%	43%
Boceprevir+PEG-IFN-2a+RBV	25%	30%	30%	32%	32%
PEG-IFN-2a+RBV	40%	30%	25%	23%	23%
PEG-IFN-2b+RBV	5%	5%	5%	2%	2%
GT1: TN mono-infected IFN unsuitable (cirrhotic and non-cirrhotic)					
NT	*100%*	*100%*	*100%*	*100%*	*100%*

PEG-IFN, Pegylated interferon α; RBV, Ribavirin; SOF, Sofosbuvir; TN, Treatment-naïve; TE, Treatment-experienced; IFN, Interferon; GT, Genotype
Source: Gilead

Table 95 Estimated market share for five years – world without SOF – GT2

	2014	**2015**	**2016**	**2017**	**2018**
GT2: TN mono-infected eligible for IFN (cirrhotic and non-cirrhotic)					
PEG-IFN-2a+RBV	75%	75%	75%	75%	75%
PEG-IFN-2b+RBV	25%	25%	25%	25%	25%
GT2: TN unsuitable to IFN (cirrhotic and non-cirrhotic)					
NT†	100%	100%	100%	100%	100%
GT2: TE mono-infected eligible for IFN (cirrhotic and non-cirrhotic)					
PEG-IFN-2a+RBV	75%	75%	75%	75%	75%
PEG-IFN-2b+RBV	25%	25%	25%	25%	25%
NT	0%	0%	0%	0%	0%
GT2: TE, unsuitable to IFN (cirrhotic and non-cirrhotic)					
NT†	100%	100%	100%	100%	100%

PEG-IFN, Pegylated interferon α; HIV, Human immunodeficiency virus; RBV, Ribavirin; NT, No treatment; SOF, Sofosbuvir; TN, Treatment-naïve; TE, Treatment-experienced; IFN, Interferon; GT, Genotype
Source: Gilead
†: Assumption

Table 96 Estimated market share for five years – world without SOF – GT3

	2014	**2015**	**2016**	**2017**	**2018**
GT3: TN mono-infected eligible for IFN (cirrhotic and non-cirrhotic)					
PEG-IFN-2a+RBV	75%	75%	75%	75%	75%
PEG-IFN-2b+RBV	25%	25%	25%	25%	25%
GT3: TN unsuitable to IFN (cirrhotic and non-cirrhotic)					
NT†	100%	100%	100%	100%	100%
GT3: TE mono-infected eligible for IFN (cirrhotic and non-cirrhotic)					
PEG-IFN-2a+RBV	75%	75%	75%	75%	75%
PEG-IFN-2b+RBV	25%	25%	25%	25%	25%
NT	0%	0%	0%	0%	0%
GT3: TE, unsuitable for IFN (cirrhotic and non-cirrhotic)					
NT†	100%	100%	100%	100%	100%

PEG-IFN, Pegylated interferon α; HIV, Human immunodeficiency virus; RBV, Ribavirin; NT, No treatment; TN, Treatment-naïve; TE, Treatment-experienced; IFN, Interferon; GT, Genotype
Source: Gilead
†: Assumption

Table 97 Estimated market share for five years – world without SOF – GT4/5/6

	2014	2015	2016	2017	2018
GT4/5/6: TN mono-infected IFN eligible (cirrhotic and non-cirrhotic)					
PEG-IFN-2a+RBV	75%	75%	75%	75%	75%
PEG-IFN-2b+RBV	25%	25%	25%	25%	25%

PEG-IFN, Pegylated interferon α; RBV, Ribavirin; NT, No treatment; SOF, Sofosbuvir; IFN, Interferon; TN, Treatment-naïve; TE, Treatment-experienced; GT, Genotype
Source: Gilead
†: Assumption

8.3 What assumption(s) were made about market share (when relevant)?

In both treatment-naïve and treatment-experienced patient populations, we have assumed that Sofosbuvir could be the main treatment option once it is approved (see Table 98 to Table 101).

Table 98 Estimated market share for five years – world with SOF – GT1

	2014	2015	2016	2017	2018
GT1: TN mono-infected IFN eligible (cirrhotic and non-cirrhotic)					
Telaprevir+PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
Boceprevir+PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
PEG-IFN-2b+RBV	XXX	XXX	XXX	XXX	XXX
SOF+PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
GT1: TN mono-infected IFN unsuitable (cirrhotic only)					
SOF+RBV	XXX	XXX	XXX	XXX	XXX
NT	XXX	XXX	XXX	XXX	XXX

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; NT, No treatment; SOF, Sofosbuvir; TN, Treatment-naïve; TE, Treatment-experienced; IFN, Interferon; GT, Genotype

Table 99 Estimated market share for five years – world with SOF – GT2

	2014	2015	2016	2017	2018
GT2: TN mono-infected IFN eligible (cirrhotic and non-cirrhotic)					
PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
PEG-IFN-2b+RBV	XXX	XXX	XXX	XXX	XXX
SOF+RBV	XXX	XXX	XXX	XXX	XXX
GT2: TN unsuitable to IFN (cirrhotic and non-cirrhotic)					

	2014	2015	2016	2017	2018
SOF+RBV	XXX	XXX	XXX	XXX	XXX
NT	XXX	XXX	XXX	XXX	XXX
GT2: TE mono-infected IFN eligible (cirrhotic and non-cirrhotic)					
PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
PEG-IFN-2b+RBV	XXX	XXX	XXX	XXX	XXX
SOF+RBV	XXX	XXX	XXX	XXX	XXX
NT	XXX	XXX	XXX	XXX	XXX
GT2: TE, unsuitable for IFN (cirrhotic and non-cirrhotic)					
SOF+RBV	XXX	XXX	XXX	XXX	XXX
NT	XXX	XXX	XXX	XXX	XXX

HIV, Human immunodeficiency virus; PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; NT, No treatment; SOF, Sofosbuvir; TN, Treatment-naïve; TE, Treatment-experienced; IFN, Interferon; GT, Genotype
Source: Gilead

Table 100 Estimated market share for five years – world with SOF - GT3

	2014	2015	2016	2017	2018
GT3: TN mono-infected IFN eligible (cirrhotic and non-cirrhotic)					
PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
PEG-IFN-2b+RBV	XXX	XXX	XXX	XXX	XXX
SOF+PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
GT3: TN unsuitable to IFN (cirrhotic and non-cirrhotic)					
SOF+RBV	XXX	XXX	XXX	XXX	XXX
NT	XXX	XXX	XXX	XXX	XXX
GT3: TE mono-infected IFN eligible (cirrhotic and non-cirrhotic)					
PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
PEG-IFN-2b+RBV	XXX	XXX	XXX	XXX	XXX
SOF+PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
NT	XXX	XXX	XXX	XXX	XXX
GT3: TE , unsuitable for IFN (cirrhotic and non-cirrhotic)					
SOF+RBV	XXX	XXX	XXX	XXX	XXX
NT	XXX	XXX	XXX	XXX	XXX

HIV, Human immunodeficiency virus; PEG-IFN, Pegylated interferon α; RBV, Ribavirin; NT, No treatment; SOF, Sofosbuvir; TN, Treatment-naïve; TE, Treatment-experienced; IFN, Interferon; GT, Genotype
Source: Gilead

Table 101 Estimated market share for five years – world with SOF – GT4/5/6

	2014	2015	2016	2017	2018
GT4/5/6: TN mono-infected IFN eligible (cirrhotic and non-cirrhotic)					
PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX
PEG-IFN-2b+RBV	XXX	XXX	XXX	XXX	XXX
SOF+PEG-IFN-2a+RBV	XXX	XXX	XXX	XXX	XXX

PEG-IFN, Pegylated interferon α; RBV, Ribavirin; NT, No treatment; SOF, Sofosbuvir; TN, Treatment-naïve; TE, Treatment-experienced; IFN, Interferon; GT, Genotype
Source: Gilead

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).

In addition to drug costs, the cost of each regimen includes monitoring costs during active treatment, adverse events management costs and costs of follow-up. These costs are detailed in sections 7.5.1 and 7.5.7.

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?

The following inputs were considered:

- Treatment costs: expected weeks of treatment, drug dosage, drug costs
- Monitoring during active treatment: expected weeks of treatment, costs of tests and visits during treatment
- Adverse events management costs: adverse events rates, treatment strategy for each adverse event, cost of each strategy including medication and outpatient visits
- Follow-up costs: management of untreated patients on waiting list (costs of managing cirrhotic and non-cirrhotic patients), management of SVR patients, management of non-SVR patients that are at risk of disease progression (cost of managing cirrhotic and non-cirrhotic patients, management of advanced liver disease, cost of liver transplant)

The unit costs for the above inputs can be found in section 7.5. Drug unit costs were sourced from the BNF (2012)[187]. Personal and social service costs were sourced from the PSSRU[190] and the inflation rate used was obtained from the HCHS Pay and Price Index[190].

8.6 Were there any estimates of resource savings? If so, what were they?

There are several sources of cost savings associated with the introduction of sofosbuvir depending on the indication considered. The treatment duration of sofosbuvir is shorter than current options which should result in a decrease of the costs of monitoring during active treatment (applicable to all genotypes). Sofosbuvir regimens are also associated with a tolerable safety profile. No adverse drug reactions specific to sofosbuvir have been identified. In practice, it should lead to a reduction of the costs of managaging adverse events, particularly in genotype 1 patients eligible for interferon who are at risk of experiencing severe adverse events when receiving protease inihibitors. During 2013, data was collected from a single UK centre to measure the patient management costs of triple therapy with protease inhibitors which estimated that management costs could be upto 6 times higher than that reported in HTA submissions (abstract submitted for APASL 2014). This suggests that the cost of managing patients with protease inhibitors in clinical practice is significantly higher than the figures being used within our submission suggesting a

conservative approach. More importantly, since sofosbuvir is associated with higher SVR rates, the costs associated with the management of non-SVR patients are projected to decrease. Finally, for patients unsuitable to IFN for which no option is currently available, the introduction of sofosbuvir should decrease the costs of managing patients on waiting list. Costs savings by genotype, fibrosis staging (cirrhotic or non-cirrhotic) and treatment history status are shown in Table 102 to Table 113.

Table 102. Cost savings in a world with SOF (All GT; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
Adverse Event costs	-£92,348	-£125,799	-£167,701	-£179,209	-£191,493
Monitoring costs	-£1,772,897	-£3,136,513	-£3,811,100	-£4,177,484	-£4,460,667
Costs of managing patients on waiting lists	-£560,957	-£913,778	-£1,139,626	-£1,346,153	-£1,542,942
TOTAL cost of managing non-SVR patients	£0	-£181,321	-£634,911	-£1,355,334	-£2,205,320

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment Naïve; SOF, Sofosbuvir; GT, Genotype

Table 103. Cost savings in a world with SOF (GT1 - TN mono-infected IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
Adverse Event costs	-£11,718	-£28,461	-£53,459	-£55,722	-£60,190
Monitoring costs	-£384,061	-£923,243	-£1,217,871	-£1,414,596	-£1,524,812
Costs of managing patients on waiting lists	£0	£0	£0	£0	£0
TOTAL cost of managing non-SVR patients	£0	-£68,712	-£249,228	-£490,342	-£752,641

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

Table 104. Cost savings in a world with SOF (GT1 - TN mono-infected unsuitable for IFN; cirrhotic patients only)

	2014	2015	2016	2017	2018
Adverse Event costs	£11	£10	£3	£3	£3
Monitoring costs	£82,131	£70,997	£24,785	£20,298	£19,977
Costs of managing patients on waiting lists	-£128,203	-£210,032	-£241,960	-£269,077	-£295,882

	2014	2015	2016	2017	2018
TOTAL cost of managing non-SVR patients	£0	£96,107	£211,284	£309,276	£389,939

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

Table 105. Cost savings in a world with SOF (GT2 - TN mono-infected IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
Adverse Event costs	-£12,529	-£16,165	-£18,533	-£20,224	-£21,449
Monitoring costs	-£95,143	-£118,866	-£136,064	-£148,265	-£157,073
Costs of managing patients on waiting lists	£0	£0	£0	£0	£0
TOTAL cost of managing non-SVR patients	£0	-£18,592	-£41,226	-£72,779	-£110,742

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

Table 106. Cost savings in a world with SOF (GT2 TN mono-infected unsuitable for IFN; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
Adverse Event costs	£5	£2	£2	£2	£2
Monitoring costs	£75,516	£28,339	£28,193	£28,343	£28,526
Costs of managing patients on waiting lists	-£67,920	-£88,290	-£108,383	-£128,570	-£148,888
TOTAL cost of managing non-SVR patients	£0	£4,126	£5,880	£8,263	£10,746

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

Table 107. Cost savings in a world with SOF (GT2 - TE mono-infected IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
Adverse Event costs	-£2,476	-£4,014	-£3,811	-£3,733	-£3,924
Monitoring costs	-£49,148	-£87,332	-£84,052	-£83,478	-£89,462

	2014	2015	2016	2017	2018
Costs of managing patients on waiting lists	£0	-£10,307	-£18,299	-£25,469	-£31,501
TOTAL cost of managing non-SVR patients	£0	-£15,631	-£49,762	-£89,965	-£128,302

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

Table 108. Cost savings in a world with SOF (GT2 - TE mono-infected unsuitable for IFN; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
Adverse Event costs	£1	£1	£0	£0	£0
Monitoring costs	£7,888	£14,877	£6,105	£3,626	£2,672
Costs of managing patients on waiting lists	-£11,633	-£25,489	-£30,171	-£33,112	-£35,587
TOTAL cost of managing non-SVR patients	£0	£687	£2,548	£3,578	£4,262

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

Table 109. Cost savings in a world with SOF (GT3 - TN mono-infected IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
Adverse Event costs	£12,492	£16,836	£19,418	£21,260	£22,592
Monitoring costs	-£409,263	-£534,119	-£615,115	-£672,458	-£713,777
Costs of managing patients on waiting lists	£0	£0	£0	£0	£0
TOTAL cost of managing non-SVR patients	£0	-£153,029	-£342,321	-£611,192	-£934,261

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

Table 110. Cost savings in a world with SOF (GT3 - TN mono-infected unsuitable for IFN; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
Adverse Event costs	£53	£20	£20	£20	£20

	2014	2015	2016	2017	2018
Monitoring costs	£395,575	£148,451	£147,687	£148,473	£149,433
Costs of managing patients on waiting lists	-£292,163	-£379,785	-£466,216	-£553,052	-£640,452
TOTAL cost of managing non-SVR patients	£0	£22,046	£31,221	£44,012	£57,061

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

Table 111. Cost savings in a world with SOF (GT3 - TE mono-infected IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
Adverse Event costs	£3,018	£2,544	-£2,383	-£6,367	-£9,513
Monitoring costs	-£257,878	-£492,331	-£541,543	-£574,509	-£639,925
Costs of managing patients on waiting lists	£0	-£82,230	-£145,715	-£202,986	-£251,058
TOTAL cost of managing non-SVR patients	£0	-£77,852	-£262,255	-£506,229	-£752,804

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

Table 112. Cost savings in a world with SOF (GT3 - TE mono-infected unsuitable for IFN; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
Adverse Event costs	£6	£12	£5	£3	£2
Monitoring costs	£50,397	£95,650	£40,953	£25,038	£19,215
Costs of managing patients on waiting lists	-£61,038	-£136,152	-£164,145	-£183,036	-£199,760
TOTAL cost of managing non-SVR patients	£0	£14,413	£57,682	£81,305	£96,329

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

Table 113. Cost savings in a world with SOF (GT4/5/6 - TN mono-infected IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018

	2014	2015	2016	2017	2018
Adverse Event costs	£1,902	£2,042	£2,322	£2,513	£2,638
Monitoring costs	-£141,484	-£151,679	-£169,448	-£182,526	-£191,296
Costs of managing patients on waiting lists	£0	£0	£0	£0	£0
TOTAL cost of managing non-SVR patients	£0	-£26,749	-£57,350	-£97,336	-£146,224

PEG-IFN, Pegylated interferon α; PI, Protease Inhibitor; RBV, Ribavirin; SVR, Sustained Virological Response; TN, Treatment-naïve; TE: Treatment-experienced; SOF, Sofosbuvir; GT, Genotype

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Assuming sofosbuvir achieves the robust market share assumptions detailed in Section 8.3, the total annual budget impact of sofosbuvir on the NHS has been estimated at £108.3 million on average over the 5 years. This incremental budget is partially explained by the higher number of patients treated in the World with sofosbuvir (about 1,000 additional patients over the 5 years). Patients that were unable to tolerate current treatment options (unsuitable to interferon) and on waiting list for a long time, could benefit from anti-viral therapy in this new context. The accrual of budget impact over 5 years is shown in Table 114. The budget impact of the introduction of sofosbuvir onto the NHS by genotype, fibrosis staging (cirrhotic or non-cirrhotic) and treatment history is shown in Table 114 to Table 125.

Table 114 Estimated annual budget impact over five years for the NHS in England and Wales (All GT; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£73,824,891	£83,041,670	£99,397,132	£113,068,406	£123,629,926
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype

Table 115 Estimated annual budget impact over five years for the NHS in England and Wales (GT1; TN mono-infected IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£31,701,609	£38,589,835	£48,618,215	£56,970,546	£62,328,119
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype; TN, Treatment-naïve; TE, Treatment-experienced

Table 116 Estimated annual budget impact over five years for the NHS in England and Wales (GT1; TN unsuitable for IFN; cirrhotic patients only)

	2014	2015	2016	2017	2018

	2014	2015	2016	2017	2018
World without SOF	£202,946	£229,202	£255,665	£282,323	£309,164
World with SOF	XXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

FN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype; TN, Treatment-naïve

Table 117 Estimated annual budget impact over five years for the NHS in England and Wales (GT2; TN IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£2,813,204	£2,661,538	£3,182,504	£3,626,494	£4,015,120
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype; TN, Treatment-naïve;

Table 118 Estimated annual budget impact over five years for the NHS in England and Wales (GT2; TN unsuitable for IFN; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£82,420	£102,384	£122,507	£142,777	£163,187
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype; TN, Treatment-naïve

Table 119 Estimated annual budget impact over five years for the NHS in England and Wales (GT2; TE IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£654,791	£993,980	£962,038	£985,983	£1,070,421
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype;TE, Treatment-experienced

Table 120 Estimated annual budget impact over five years for the NHS in England and Wales (GT2; TE unsuitable for IFN; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£30,150	£32,362	£33,981	£35,809	£37,768

	2014	2015	2016	2017	2018
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype; TE, Treatment-experienced

Table 121 Estimated annual budget impact over five years for the NHS in England and Wales (GT3; TN IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£12,101,181	£12,064,818	£14,613,306	£16,867,978	£18,898,426
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; TN, Treatment-naïve

Table 122 Estimated annual budget impact over five years for the NHS in England and Wales (GT3; TN unsuitable for IFN; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£354,536	£440,413	£526,970	£614,163	£701,958
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype; TN, Treatment-naïve

Table 123 Estimated annual budget impact over five years for the NHS in England and Wales (GT3;TE IFN eligible; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£3,435,666	£5,515,136	£5,788,232	£6,200,808	£6,942,240
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype

Table 124 Estimated annual budget impact over five years for the NHS in England and Wales (GT3; TE unsuitable for IFN; cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£158,195	£173,855	£185,550	£198,801	£213,015
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype; TE, Treatment-experienced

Table 125 Estimated annual budget impact over five years for the NHS in England and Wales (GT4/5/6; TN cirrhotic and non-cirrhotic patients)

	2014	2015	2016	2017	2018
World without SOF	£2,619,141	£2,729,744	£3,190,050	£3,562,964	£3,871,019
World with SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Annual budget impact of SOF	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

IFN, Interferon; NHS, National Health Service; SOF, Sofosbuvir; GT, Genotype; TN, Treatment-naïve

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The short time horizon of the budget impact model fails to capture savings caused by avoiding more severe health states that take a longer time to occur, such as decompensated cirrhosis, hepatocellular carcinoma and liver transplants. We have also not included any of the costs associated with the development of extra-hepatic manifestations as a result of HCV such as diabetes.

In the case of sofosbuvir as an all oral treatments this could results in a reduction inmonitoring costs and a change in the way patients are treated and monitored potentially resulting in savings for the NHS. The introduction of sofosbuvir will tend to reduce the resource use around the management of HCV patients and thereby freeing up capacity within the HCV health service.

The long term outcomes could mean also an eradication to HCV-induced hepatocellular carcinoma and HCV-related liver transplant, since both of these events stem from cirrhotic patients which have to date proven to be a very difficult to treat population.

In addition, the higher SVR rates induce to some extent a long-term public health benefit by preventing onwards transmission in higher risk population and therefore reduce future HCV prevalence. However, this benefit is hardly possible to capture in a budget impact model.

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